

\$FILE 'USPAT' ENTERED AT 07:40:25 ON 24 SEP 1998

=> s erbb2 or her2

71 ERBB2

138 HER2

L1 184 ERBB2 OR HER2

=> s l1 and antibod?

30425 ANTIBOD?

L2 172 L1 AND ANTIBOD?

=> s l2 and ((cell death) or apopt?)

213374 CELL

19940 DEATH

2424 CELL DEATH

(CELL(W)DEATH)

535 APOPT?

L3 42 L2 AND ((CELL DEATH) OR APOPT?)

=> d bib ab 1-

US PAT NO: 5,811,098 [IMAGE AVAILABLE] L3: 1 of 42

DATE ISSUED: Sep. 22, 1998

TITLE: \*\*Antibodies\*\* to HER4, human receptor tyrosine kinase

INVENTOR: Gregory D. Plowman, San Carlos, CA

Jean-Michel Culouscou, Seattle, WA

Mohammed Shoyab, Seattle, WA

Clay B. Siegall, Seattle, WA

Ingegerd Hellstrom, Seattle, WA

Karl E. Hellstrom, Seattle, WA

ASSIGNEE: Bristol-Myers Squibb Company, New York, NY (U.S. corp.)

APPL-NO: 08/484,438

DATE FILED: Jun. 7, 1995

ART-UNIT: 188

PRIM-EXMR: Paula K. Hutzell

ASST-EXMR: Heather A. Bakalyar

LEGAL-REP: Brian Poor, Thomas R. Savitsky

US PAT NO: 5,811,098 [IMAGE AVAILABLE] L3: 1 of 42

ABSTRACT:

The molecular cloning, expression, and biological characteristics of a novel receptor tyrosine kinase related to the epidermal growth factor receptor, termed HER4/p180.sup.erbB4, are described. \*\*Antibodies\*\* to HER4 are disclosed. A HER4 ligand capable of inducing cellular differentiation of breast cancer cells is also disclosed. In view of the expression of HER4 in several human cancers and in certain tissues of neuronal and muscular origin, various diagnostic and therapeutic uses of HER4-derived and HER4-related biological compositions are provided.

US PAT NO: 5,801,181 [IMAGE AVAILABLE] L3: 2 of 42

DATE ISSUED: Sep. 1, 1998

TITLE: Amino alcohol substituted cyclic compounds

INVENTOR: John Michnick, Seattle, WA

Gail E. Underiner, Brier, WA

J. Peter Klein, Vashon Island, WA

Glenn C. Rice, Seattle, WA

ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)

APPL-NO: 08/474,820  
DATE FILED: Jun. 7, 1995  
ART-UNIT: 166  
PRIM-EXMR: Jose G. Dees  
ASST-EXMR: Alton Pryor  
LEGAL-REP: McDermott Will & Emery

US PAT NO: 5,801,181 [IMAGE AVAILABLE] L3: 2 of 42

ABSTRACT:

Therapeutic compounds have the formula:

(X)<sub>j</sub>--(core moiety),  
J being an integer from one to three, the core moiety having at least one, five- to seven-membered ring and X being a racemic mixture, R or S enantiomer, solvate, hydrate, or salt of: ##STR1## \*C is a chiral carbon atom, n is an integer from one to four (preferably from one to three), one or more carbon atoms of (CH<sub>2</sub>)<sub>n</sub> may be substituted by a keto or hydroxy group, and m is an integer from one to fourteen. Independently, R<sub>1</sub> and R<sub>2</sub> may be a hydrogen, a straight or branched chain alkane or alkene of up to twelve carbon atoms in length, or --(CH<sub>2</sub>)<sub>w</sub> R<sub>5</sub>, w being an integer from two to fourteen and R<sub>5</sub> being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R<sub>5</sub> being hydroxy, chloro, fluoro, bromo, or C<sub>1-6</sub> alkoxy. Or jointly, R<sub>1</sub> and R<sub>2</sub> form a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon atoms, N being a hetero atom. R<sub>3</sub> is a hydrogen or C<sub>1-3</sub>. Or, therapeutic compounds may also have the formula: ##STR2## R<sub>4</sub> is a hydrogen, a straight or branched chain alkane or alkene of up to eight carbon atoms in length, --(CH<sub>2</sub>)<sub>w</sub> R<sub>5</sub>, w being an integer from two to fourteen and R<sub>5</sub> being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R<sub>5</sub> being hydroxy, chloro, fluoro, bromo, or C<sub>1-6</sub> alkoxy, or a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon atoms, N being a hetero atom. r and s are independently integers from one to four, the sum (r+s) not being greater than five. t is an integer from one to fourteen and one or more carbon atoms of (CH<sub>2</sub>)<sub>s</sub> or (CH<sub>2</sub>)<sub>t</sub> may be substituted by a keto or hydroxy group.

US PAT NO: 5,798,374 [IMAGE AVAILABLE] L3: 3 of 42  
DATE ISSUED: Aug. 25, 1998  
TITLE: Methods of inhibiting phosphatase activity and treatment of disorders associated therewith  
INVENTOR: Peng Cho Tang, Moraga, CA  
Gerald McMahon, Kenwood, CA  
ASSIGNEE: Sugan Inc., Redwood City, CA (U.S. corp.)  
APPL-NO: 08/481,954  
DATE FILED: Jun. 7, 1995  
ART-UNIT: 163  
PRIM-EXMR: Robert Gerstl  
LEGAL-REP: Pennie & Edmonds LLP

US PAT NO: 5,798,374 [IMAGE AVAILABLE] L3: 3 of 42

ABSTRACT:

The present invention relates to organic molecules capable of inhibiting protein tyrosine phosphatase activity. The invention further relates to the use of such molecules to modulate or regulate signal transduction by inhibiting protein tyrosine phosphatase activity. Finally, the invention relates to the use of such molecules to treat various disease states including diabetes mellitus.

US PAT NO: 5,792,772 [IMAGE AVAILABLE] L3: 4 of 42

DATE ISSUED: Aug. 11, 1998

TITLE: Enantiomerically pure hydroxylated xanthine compounds

INVENTOR: James A. Bianco, Seattle, WA

Paul Woodson, Bothell, WA

David Porubek, Edmonds, WA

Jack Singer, Seattle, WA

ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)

APPL-NO: 08/458,957

DATE FILED: Jun. 1, 1995

ART-UNIT: 125

PRIM-EXMR: Theodore J. Criares

LEGAL-REP: Foley & Lardner

US PAT NO: 5,792,772 [IMAGE AVAILABLE] L3: 4 of 42

ABSTRACT:

There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

US PAT NO: 5,789,245 [IMAGE AVAILABLE] L3: 5 of 42

DATE ISSUED: Aug. 4, 1998

TITLE: Alphavirus structural protein expression cassettes

INVENTOR: Thomas W. Dubensky, Jr., Rancho Sante Fe, CA

John M. Polo, San Diego, CA

Carlos E. Ibanez, San Diego, CA

Stephen M. W. Chang, San Diego, CA

Douglas J. Jolly, Leucadia, CA

David A. Driver, San Diego, CA

ASSIGNEE: Chiron Corporation, Emeryville, CA (U.S. corp.)

APPL-NO: 08/741,881

DATE FILED: Oct. 30, 1996

ART-UNIT: 126

PRIM-EXMR: James Ketter

ASST-EXMR: John S. Brusca

LEGAL-REP: David D. McMasters, Norman J. Kruse, Robert P. Blackburn

US PAT NO: 5,789,245 [IMAGE AVAILABLE] L3: 5 of 42

ABSTRACT:

The present invention provides compositions and methods for utilizing recombinant alphavirus vectors. Also disclosed are compositions and methods for making and utilizing eukaryotic layered vector initiation systems.

US PAT NO: 5,783,186 [IMAGE AVAILABLE] L3: 6 of 42

DATE ISSUED: Jul. 21, 1998

TITLE: \*\*Antibody\*\*-induced \*\*apoptosis\*\*

INVENTOR: Tsutomu Arakawa, Thousand Oaks, CA

Yoshiko Kita, Thousand Oaks, CA

ASSIGNEE: Amgen Inc., Thousand Oaks, CA (U.S. corp.)

APPL-NO: 08/568,072

DATE FILED: Dec. 5, 1995

ART-UNIT: 186

PRIM-EXMR: Toni R. Scheiner

ASST-EXMR: Nancy A. Johnson

LEGAL-REP: Robert B. Winter, Steven M. Odre, Ron K. Levy

US PAT NO: 5,783,186 [IMAGE AVAILABLE] L3: 6 of 42

ABSTRACT:

Anti-**Her2** **antibodies** which induce **apoptosis** in **Her2** expressing cells are disclosed. The **antibodies** are used to "tag" **Her2** overexpressing tumors for elimination by the host immune system. Also disclosed are hybridoma cell lines producing the **antibodies**, methods for treating cancer using the **antibodies**, and pharmaceutical compositions.

US PAT NO: 5,777,117 [IMAGE AVAILABLE] L3: 7 of 42

DATE ISSUED: Jul. 7, 1998

TITLE: Method for preparing substituted amino alcohol compounds

INVENTOR: J. Peter Klein, Vashon, WA

Gail E. Underiner, Brier, WA

Anil M. Kumar, Seattle, WA

ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)

APPL-NO: 08/472,569

DATE FILED: Jun. 7, 1995

ART-UNIT: 129

PRIM-EXMR: Jose G. Dees

ASST-EXMR: Mary C. Cebulak

LEGAL-REP: McDermott, Will & Emery

US PAT NO: 5,777,117 [IMAGE AVAILABLE] L3: 7 of 42

ABSTRACT:

Disclosed is a process for preparing compounds having a straight or branched aliphatic hydrocarbon structure of formula I: **STR1** In formula I, n is an integer from one to four and m is an integer from four to twenty. Independently, R.sub.1 and R.sub.2 are hydrogen, a straight or branched chain alkyl, alkenyl or alkynyl of up to twenty carbon atoms in length or --(CH.sub.2).sub.w R.sub.5. If R.sub.1 or R.sub.2 is --(CH.sub.2).sub.w R.sub.5, w may be an integer from one to twenty and

R.sub.5 may be an hydroxyl, halo, C.sub.1-8 alkoxyl group or a substituted or unsubstituted carbocycle or heterocycle. Alternatively, R.sub.1 and R.sub.2 may jointly form a substituted or unsubstituted, saturated or unsaturated heterocycle having from four to eight carbon atoms, N being a hetero atom of the resulting heterocycle. R.sub.3 may be either hydrogen or C.sub.1-3. In the compounds, a total sum of carbon atoms comprising R.sub.1 or R.sub.2, (CH.sub.2).sub.n and (CH.sub.2).sub.m does not exceed forty. R.sub.4 is a terminal moiety comprising a substituted or unsubstituted, oxidized or reduced ring system, the ring system having a single ring or two to three fused rings, a ring comprising from three to seven ring atoms. The disclosed compounds are effective agents to inhibit undesirable responses to cell stimuli.

US PAT NO: 5,776,427 [IMAGE AVAILABLE] L3: 8 of 42  
DATE ISSUED: Jul. 7, 1998  
TITLE: Methods for targeting the vasculature of solid tumors  
INVENTOR: Philip E. Thorpe, Dallas, TX  
Francis J. Burrows, San Diego, CA  
ASSIGNEE: Board of Regents, The University of Texas System, Austin,  
TX (U.S. corp.)  
APPL-NO: 08/456,495  
DATE FILED: Jun. 1, 1995  
ART-UNIT: 121  
PRIM-EXMR: John Kight  
ASST-EXMR: Michael G. Hartley  
LEGAL-REP: Arnold, White & Durkee

US PAT NO: 5,776,427 [IMAGE AVAILABLE] L3: 8 of 42

ABSTRACT:

The present invention relates generally to methods and compositions for targeting the vasculature of solid tumors using immunological- and growth factor-based reagents. In particular aspects, **antibodies** carrying diagnostic or therapeutic agents are targeted to the vasculature of solid tumor masses through recognition of tumor vasculature-associated antigens, such as, for example, through endoglin binding, or through the specific induction of endothelial cell surface antigens on vascular endothelial cells in solid tumors.

US PAT NO: 5,770,421 [IMAGE AVAILABLE] L3: 9 of 42  
DATE ISSUED: Jun. 23, 1998  
TITLE: Human ALK protein tyrosine kinase  
INVENTOR: Stephan W. Morris, Memphis, TN  
A. Thomas Look, Memphis, TN  
ASSIGNEE: St. Jude Children's Research Hospital, Memphis, TN (U.S. corp.)  
APPL-NO: 08/542,363  
DATE FILED: Oct. 12, 1995  
ART-UNIT: 184  
PRIM-EXMR: Keith D. Hendricks  
LEGAL-REP: Sterne, Kessler, Goldstein & Fox P.L.L.C.

US PAT NO: 5,770,421 [IMAGE AVAILABLE] L3: 9 of 42

ABSTRACT:

The present invention is based on the identification and sequence determination of a novel gene, ALK, which is fused to the gene encoding nucleophosmin (NPM) in translocations present in t(2;5) lymphoma cells. Based on homologies to other proteins, the amino acid sequence of the polypeptide encoded by the ALK (Anaplastic Lymphoma Kinase) gene is a membrane-spanning protein tyrosine kinase (PTK)/receptor. **\*\*Antibodies\*\*** to the ALK PTK/receptor and methods utilizing such **\*\*antibodies\*\*** are described, as are methods of using the ALK gene to isolate ligands for the ALK PTK/receptor.

US PAT NO: 5,763,217 [IMAGE AVAILABLE] L3: 10 of 42  
DATE ISSUED: Jun. 9, 1998  
TITLE: Method of using, process of preparing and composition  
comprising recombinant herpesvirus vectors  
INVENTOR: Max Cynader, Vancouver, Canada  
Francis Tufaro, Vancouver, Canada  
ASSIGNEE: University of British Columbia, Vancouver, Canada (foreign  
corp.)  
APPL-NO: 08/540,692  
DATE FILED: Oct. 11, 1995  
ART-UNIT: 185  
PRIM-EXMR: David Guzo  
ASST-EXMR: Johnny F. Railey, II  
LEGAL-REP: Seed and Berry LLP

US PAT NO: 5,763,217 [IMAGE AVAILABLE] L3: 10 of 42

ABSTRACT:

Methods for treatment, processes for preparing, and compositions for delivering selected nucleic acid sequences to cells, primarily of the treatment of neurological disorders and exploring neurological functions, are disclosed. In particular, the invention provides recombinant Herpesvirus vectors with a high rate of expression of selected nucleic acid sequences and/or a low cytopathicity and its associated methods and processes.

US PAT NO: 5,756,291 [IMAGE AVAILABLE] L3: 11 of 42  
DATE ISSUED: May 26, 1998  
TITLE: Aptamers specific for biomolecules and methods of making  
INVENTOR: Linda Griffin, Atherton, CA  
Glenn Albrecht, Redwood City, CA  
John Latham, Palo Alto, CA  
Lawrence Leung, Hillsborough, CA  
Eric Vermaas, Oakland, CA  
John J. Toole, Burlingame, CA  
ASSIGNEE: Gilead Sciences, Inc., Foster City, CA (U.S. corp.)  
APPL-NO: 08/484,192  
DATE FILED: Jun. 7, 1995  
ART-UNIT: 187  
PRIM-EXMR: Stephanie W. Zitomer  
LEGAL-REP: Mark L. Bosse

US PAT NO: 5,756,291 [IMAGE AVAILABLE]

L3: 11 of 42

ABSTRACT:

A method for identifying oligomer sequences, optionally comprising modified base, which specifically bind target molecules such as serum proteins, kinins, eicosanoids and extracellular proteins is described. The method is used to generate aptamers that bind to serum Factor X, PDGF, FGF, ICAM, VCAM, E-selectin, thrombin, bradykinin, PGF2 and cell surface molecules. The technique involves complexation of the target molecule with a mixture of oligonucleotides containing random sequences and sequences which serve as primer for PCR under conditions wherein a complex is formed with the specifically binding sequences, but not with the other members of the oligonucleotide mixture. The complex is then separated from uncomplexed oligonucleotides and the complexed members of the oligonucleotide mixture are recovered from the separated complex using the polymerase chain reaction. The recovered oligonucleotides may be sequenced, and successive rounds of selection using complexation, separation, amplification and recovery can be employed. The oligonucleotides can be used for therapeutic and diagnostic purposes and for generating secondary aptamers.

US PAT NO: 5,750,575 [IMAGE AVAILABLE]

L3: 12 of 42

DATE ISSUED: May 12, 1998

TITLE: Substituted amino alcohol compounds

INVENTOR: J. Peter Klein, Vashon, WA

Gail E. Underiner, Brier, WA

Anil M. Kumar, Seattle, WA

ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)

APPL-NO: 08/475,721

DATE FILED: Jun. 7, 1995

ART-UNIT: 129

PRIM-EXMR: Jose G. Dees

ASST-EXMR: M. Cebulak

LEGAL-REP: Stephen Faciszewski, Esq.

US PAT NO: 5,750,575 [IMAGE AVAILABLE]

L3: 12 of 42

ABSTRACT:

Disclosed are compounds having a straight or branched aliphatic hydrocarbon structure of formula I: ##STR1## In formula I, n is an integer from one to four and m is an integer from four to twenty. Independently, R.sub.1 and R.sub.2 are hydrogen, a straight or branched chain alkyl, alkenyl or alkynyl of up to twenty carbon atoms in length or --(CH.sub.2).sub.w R.sub.5. If R.sub.1 or R.sub.2 is --(CH.sub.2).sub.w R.sub.5, w may be an integer from one to twenty and R.sub.5 may be an hydroxyl, halo, C.sub.1-8 alkoxyl group or a substituted or unsubstituted carbocycle or heterocycle. Alternatively, R.sub.1 and R.sub.2 may jointly form a substituted or unsubstituted, saturated or unsaturated heterocycle having from four to eight carbon atoms, N being a hetero atom of the resulting heterocycle. R.sub.3 may be either hydrogen or C.sub.1-3. In the compounds, a total sum of carbon atoms comprising R.sub.1 or R.sub.2, (CH.sub.2).sub.n and (CH.sub.2).sub.m does not exceed forty. R.sub.4 is a carbocycle comprising a substituted or unsubstituted ring system, the

ring system having a single ring or two fused rings, a ring comprising from three to seven ring atoms. The disclosed compounds are effective agents to inhibit undesirable responses to cell stimuli.

US PAT NO: 5,739,138 [IMAGE AVAILABLE] L3: 13 of 42  
DATE ISSUED: Apr. 14, 1998  
TITLE: Enantiomerically pure hydroxylated xanthine compounds to treat autoimmune diabetes  
INVENTOR: James A. Bianco, Seattle, WA  
Paul Woodson, Bothell, WA  
David Porubek, Edmonds, WA  
Jack Singer, Seattle, WA  
ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)  
APPL-NO: 08/457,703  
DATE FILED: Jun. 1, 1995  
ART-UNIT: 125  
PRIM-EXMR: Theodore J. Criares  
LEGAL-REP: Stephen Faciszewski

US PAT NO: 5,739,138 [IMAGE AVAILABLE] L3: 13 of 42

ABSTRACT:

There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

US PAT NO: 5,723,333 [IMAGE AVAILABLE] L3: 14 of 42  
DATE ISSUED: Mar. 3, 1998  
TITLE: Human pancreatic cell lines: developments and uses  
INVENTOR: Fred Levine, Del Mar, CA  
Sijian Wang, San Diego, CA  
Gillian M. Beattie, Poway, CA  
Alberto Hayek, La Jolla, CA  
ASSIGNEE: Regents of The University of California, Oakland, CA (U.S. corp.)  
APPL-NO: 08/509,121  
DATE FILED: Jul. 31, 1995  
ART-UNIT: 185  
PRIM-EXMR: George G. Elliott  
ASST-EXMR: Robert Schwartzman  
LEGAL-REP: Townsend & Townsend & Crew

US PAT NO: 5,723,333 [IMAGE AVAILABLE] L3: 14 of 42

ABSTRACT:

This invention relates to cell lines, particularly mammalian cell lines, established by transforming the cells with vectors, preferably retroviral vectors, containing two or more oncogenes under the control of one or more inducible promoters and/or genetic elements. Also within the scope



of the invention are human cell lines with extended in vitro lifespan, transformed by vectors containing one or more oncogenes under the control of one or more, preferably exogenous, inducible promoters and/or genetic elements. The vectors may additionally contain gene(s) encoding for desired gene product(s). Also disclosed are insulin producing human pancreatic cell lines useful for transplantation into human diabetic patients.

US PAT NO: 5,705,614 [IMAGE AVAILABLE] L3: 15 of 42  
DATE ISSUED: Jan. 6, 1998  
TITLE: Methods of producing antigen forks  
INVENTOR: David B. Ring, Palo Alto, CA  
ASSIGNEE: Chiron Corporation, Emeryville, CA (U.S. corp.)  
APPL-NO: 08/396,595  
DATE FILED: Mar. 1, 1995  
ART-UNIT: 186  
PRIM-EXMR: Frank C. Eisenschenk  
LEGAL-REP: Paul B. Savereide, Robert P. Blackburn

US PAT NO: 5,705,614 [IMAGE AVAILABLE] L3: 15 of 42

ABSTRACT:

The present invention relates to a class of molecules called "antigen forks" that inhibit cell growth. These antigen forks possess separate binding elements for two different cell surface antigens and are believed to heterologously crosslink the antigens by binding to them. The two antigens recognized by an antigen fork differ in at least one cellular functional quality, but are simultaneously expressed on the surface of at least one cell type targeted for killing or growth inhibition. The present invention also relates to a method of assay to determine which **\*\*antibodies\*\*** may be useful in the preparation of antigen forks.

US PAT NO: 5,670,506 [IMAGE AVAILABLE] L3: 16 of 42  
DATE ISSUED: Sep. 23, 1997  
TITLE: Halogen, isothiocyanate or azide substituted xanthines  
INVENTOR: Alistair Leigh, Brier, WA  
John Michnick, Seattle, WA  
Anil Kumar, Seattle, WA  
Gail Underiner, Brier, WA  
ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)  
APPL-NO: 08/042,946  
DATE FILED: Apr. 5, 1993  
ART-UNIT: 122  
PRIM-EXMR: Mukund J. Shah  
ASST-EXMR: Pavanaram K. Sripada  
LEGAL-REP: Stephen Faciszewski

US PAT NO: 5,670,506 [IMAGE AVAILABLE] L3: 16 of 42

ABSTRACT:

There is disclosed a compound having the formula: **##STR1##** wherein n is an integer from 5 to 9, wherein the core moiety is a heterocyclic moiety wherein C.sub.a, C.sub.b, and C.sub.c are an R or S enantiomer or racemic

mixture and the C.sub.a, C.sub.b, and C.sub.c carbon atoms are bonded together by a single bond, double bond, ether or ester linkages, wherein R.sub.1, R.sub.2 and R.sub.3 are independently halo, hydroxy, hydrogen, keto, isothiocyano, azide or haloacetoxy with the proviso that at least one of R.sub.1, R.sub.2 or R.sub.3 must be a halo, isothiocyano, azide or haloacetoxy group, wherein R.sub.4 is hydrogen, C.sub.1-6 alkyl, C.sub.1-6 alkenyl, cyclo C.sub.4-6 alkyl, or phenyl, and wherein halo refers to fluoro, chloro, bromo and iodo and salts thereof and pharmaceutical compositions thereof.

US PAT NO: 5,660,827 [IMAGE AVAILABLE] L3: 17 of 42  
DATE ISSUED: Aug. 26, 1997  
TITLE: \*\*Antibodies\*\* that bind to endoglin  
INVENTOR: Philip E. Thorpe, Dallas, TX  
Francis J. Burrows, San Diego, CA  
ASSIGNEE: Board of Regents, The University of Texas System, Austin,  
TX (U.S. corp.)  
APPL-NO: 08/457,229  
DATE FILED: Jun. 1, 1995  
ART-UNIT: 186  
PRIM-EXMR: Lila Feisee  
ASST-EXMR: Ray F. Ebert  
LEGAL-REP: Arnold, White & Durkee

US PAT NO: 5,660,827 [IMAGE AVAILABLE] L3: 17 of 42

ABSTRACT:

Disclosed are \*\*antibodies\*\* that specifically bind to endoglin. Conjugates of the \*\*antibodies\*\* linked to diagnostic or therapeutic agents are also provided. Methods of using the \*\*antibodies\*\* and conjugates are also disclosed, including methods of targeting the vasculature of solid tumors through recognition of the tumor vasculature-associated antigen, endoglin.

US PAT NO: 5,652,243 [IMAGE AVAILABLE] L3: 18 of 42  
DATE ISSUED: Jul. 29, 1997  
TITLE: Methods of using enantiomerically pure hydroxylated  
xanthine compounds  
INVENTOR: James A. Bianco, Seattle, WA  
Jack Singer, Seattle, WA  
ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)  
APPL-NO: 08/343,810  
DATE FILED: Nov. 22, 1994  
ART-UNIT: 125  
PRIM-EXMR: Theodore J. Criares  
LEGAL-REP: Jeffrey B. Oster, Stephen Faciszewski

US PAT NO: 5,652,243 [IMAGE AVAILABLE] L3: 18 of 42

ABSTRACT:

There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of

3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

US PAT NO: 5,652,115 [IMAGE AVAILABLE] L3: 19 of 42  
DATE ISSUED: Jul. 29, 1997  
TITLE: Method of detecting tumors containing complexes of p53 and HSP70  
INVENTOR: Jeffrey Robert Marks, Hillsborough, NC  
James Dirk Inglehart, Durham, NC  
Andrew Mark Davidoff, Durham, NC  
Jerry G. Henslee, Libertyville, IL  
ASSIGNEE: Duke University, Durham, NC (U.S. corp.)  
APPL-NO: 08/276,872  
DATE FILED: Jul. 18, 1994  
ART-UNIT: 186  
PRIM-EXMR: Toni R. Scheiner  
LEGAL-REP: Cheryl L. Becker

US PAT NO: 5,652,115 [IMAGE AVAILABLE] L3: 19 of 42

ABSTRACT:

The present invention relates to the finding that the class of mutant p53 proteins which bind to HSP70 defines a group of mutant p53 proteins which elicit serum autoantibodies. Thus, disclosed is a method of classifying tumor cells for the ability to produce serum p53 autoantibodies in a patient carrying such tumor cells, a method of detecting tumor cells containing a mutant p53 protein capable of forming a complex with a 70 kilodalton heat shock protein (hsp70) in the cells in a patient, a method of distinguishing tumor cells capable of causing more aggressive disease in a patient carrying the tumor cells, and a method of monitoring a patient for the recurrence of disease in a patient previously diagnosed as carrying tumor cells.

US PAT NO: 5,648,357 [IMAGE AVAILABLE] L3: 20 of 42  
DATE ISSUED: Jul. 15, 1997  
TITLE: Enantiomerically pure hydroxylated xanthine compounds  
INVENTOR: James A. Bianco, Seattle, WA  
Paul Woodson, Bothell, WA  
David Porubek, Edmonds, WA  
Jack Singer, Seattle, WA  
ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)  
APPL-NO: 08/307,554  
DATE FILED: Sep. 16, 1994  
ART-UNIT: 125  
PRIM-EXMR: Theodore J. Criares  
LEGAL-REP: Jeffrey B. Oster, Stephen Faciszewski

US PAT NO: 5,648,357 [IMAGE AVAILABLE] L3: 20 of 42

ABSTRACT:

There is disclosed compounds and pharmaceutical compositions that are a

resolved R or S (preferably R) enantiomer of an .omega-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

US PAT NO: 5,643,567 [IMAGE AVAILABLE] L3: 21 of 42  
DATE ISSUED: Jul. 1, 1997  
TITLE: Methods for the suppression of neu mediated tumors by  
adenoviral E1A and SV40 large T antigen  
INVENTOR: Mien-Chie Hung, Houston, TX  
Di-Hua Yu, Houston, TX  
Angahin Matin, Houston, TX  
Yujiao Joe Zhang, Houston, TX  
ASSIGNEE: Board of Regents, The University of Texas System, Austin,  
TX (U.S. corp.)  
APPL-NO: 08/276,359  
DATE FILED: Jul. 15, 1994  
ART-UNIT: 184  
PRIM-EXMR: Deborah Crouch  
LEGAL-REP: Arnold, White & Durkee

US PAT NO: 5,643,567 [IMAGE AVAILABLE] L3: 21 of 42

ABSTRACT:

Disclosed are methods and compositions for the suppression of expression of the neu oncogene, as well as suppression of neu oncogene-mediated transformation, tumorigenesis and metastasis. The method disclosed involves introduction of adenovirus early 1A gene (the E1A gene) products, or the large T antigen (the LT gene product), or both into affected cells. These products, which are preferably introduced by transfection of the E1A gene into affected cells, serve to suppress neu gene expression as measured by a reduction of p185 expression. Furthermore, the E1A gene products surprisingly serve to suppress the oncogenic phenotype, as indicated by a reduction in cell growth, growth in soft agar, as well as tumorigenic and metastatic potential in vivo. The inventors propose that E1A gene products, LT gene products or derivatives therefrom, may ultimately be employed a treatment modalities for neu-mediated cancers, such as cancers of the female genital tract and breast. The inventors also propose methods of transfecting cells with either the E1A or the LT gene products using adenoviral vectors or liposomes.

US PAT NO: 5,641,869 [IMAGE AVAILABLE] L3: 22 of 42  
DATE ISSUED: Jun. 24, 1997  
TITLE: Method for purifying heregulin  
INVENTOR: Richard L. Vandlen, Hillsborough, CA  
William E. Holmes, Pacifica, CA  
ASSIGNEE: Genentech, Inc., South San Francisco, CA (U.S. corp.)  
APPL-NO: 08/456,201  
DATE FILED: May 31, 1995  
ART-UNIT: 187

PRIM-EXMR: Lisa B. Arthur  
LEGAL-REP: Wendy M. Lee

US PAT NO: 5,641,869 [IMAGE AVAILABLE] L3: 22 of 42

ABSTRACT:

A novel polypeptide with binding affinity for the p185.sup.\*\*HER2\*\* receptor, designated heregulin-.alpha., has been identified and purified from cultured human cells. DNA sequences encoding additional heregulin polypeptides, designated heregulin-.alpha., heregulin-.beta.1, heregulin-.beta.2, heregulin-.beta.2-like, and heregulin-.beta.3, have been isolated, sequenced and expressed. Provided herein are nucleic acid sequences encoding the amino acid sequences of heregulins useful in the production of heregulins by recombinant means. Further provided are the amino acid sequences of heregulins and purification methods therefor. Heregulins and their \*\*antibodies\*\* are useful as therapeutic agents and in diagnostic methods.

US PAT NO: 5,641,783 [IMAGE AVAILABLE] L3: 23 of 42

DATE ISSUED: Jun. 24, 1997

TITLE: Substituted amino alcohol compounds

INVENTOR: J. Peter Klein, Vashon, WA

Gail E. Underiner, Brier, WA

Anil M. Kumar, Seattle, WA

ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)

APPL-NO: 08/303,842

DATE FILED: Sep. 8, 1994

ART-UNIT: 129

PRIM-EXMR: Richard L. Raymond

ASST-EXMR: Mary C. Cebulak

LEGAL-REP: Stephen Faciszewski, Jeffrey B. Oster

US PAT NO: 5,641,783 [IMAGE AVAILABLE] L3: 23 of 42

ABSTRACT:

Disclosed are compounds having a straight or branched aliphatic hydrocarbon structure of formula I: ##STR1## In formula I, n is an integer from one to four and m is an integer from four to twenty. Independently, R.sub.1 and R.sub.2 are hydrogen, a straight or branched chain alkyl, alkenyl or alkynyl of up to twenty carbon atoms in length or --(CH.sub.2).sub.w R.sub.5. If R.sub.1 or R.sub.2 is --(CH.sub.2).sub.w R.sub.5, w may be an integer from one to twenty and R.sub.5 may be an hydroxyl, halo, C.sub.1-8 alkoxyl group or a substituted or unsubstituted carbocycle or heterocycle. Alternatively, R.sub.1 and R.sub.2 may jointly form a substituted or unsubstituted, saturated or unsaturated heterocycle having from four to eight carbon atoms, N being a hetero atom of the resulting heterocycle. R.sub.3 may be either hydrogen or C.sub.1-3. In the compounds, a total sum of carbon atoms comprising R.sub.1 or R.sub.2, (CH.sub.2).sub.n and (CH.sub.2).sub.m does not exceed forty. R.sub.4 is a terminal moiety comprising a substituted or unsubstituted, oxidized or reduced ring system, the ring system having a single ring or two to three fused rings, a ring comprising from three to seven ring atoms. The disclosed compounds are effective agents to inhibit undesirable responses to cell stimuli.

US PAT NO: 5,641,484 [IMAGE AVAILABLE] L3: 24 of 42  
DATE ISSUED: Jun. 24, 1997  
TITLE: Methods for the suppression of neu mediated tumors by  
adenoviral E1A and SV40 large T antigen  
INVENTOR: Mien-Chie Hung, Houston, TX  
Di-Hua Yu, Houston, TX  
Angabin Matin, Houston, TX  
ASSIGNEE: Board of Regents, The University of Texas System, Austin,  
TX (U.S. corp.)  
APPL-NO: 08/162,406  
DATE FILED: Dec. 3, 1993  
ART-UNIT: 184  
PRIM-EXMR: Deborah Crouch  
LEGAL-REP: Arnold, White & Durkee

US PAT NO: 5,641,484 [IMAGE AVAILABLE] L3: 24 of 42

ABSTRACT:

Disclosed are methods and compositions for the suppression of expression of the neu oncogene, as well as suppression of neu oncogene-mediated transformation, tumorigenesis and metastasis. The method disclosed involves introduction of adenovirus early 1A gene (the E1A gene) products, so to large T antigen (the LT gene product), or both into affected cells. These products, which are preferably introduced by transfection of the E1A gene into affected cells, serve to suppress neu gene expression as measured by a reduction of p185 expression. Furthermore, the E1A gene products surprisingly serve to suppress the oncogenic phenotype, as indicated by a reduction in cell growth, growth in soft agar, as well as tumorigenic and metastatic potential in vivo. The inventors propose that E1A gene products, LT gene products or derivatives therefrom, may ultimately be employed a treatment modalities for neu-mediated cancers, such as cancers of the female genital tract and breast. The inventors also propose methods of transfecting cells with either the E1A or the LT gene products using liposomes.

US PAT NO: 5,635,599 [IMAGE AVAILABLE] L3: 25 of 42  
DATE ISSUED: Jun. 3, 1997  
TITLE: Fusion proteins comprising circularly permuted ligands  
INVENTOR: Ira H. Pastan, Potomac, MD  
Robert J. Kreitman, Potomac, MD  
Raj K. Puri, North Potomac, MD  
ASSIGNEE: The United States of America as represented by the  
Department of Health and Human Services, Washington, DC  
(U.S. govt.)  
APPL-NO: 08/225,224  
DATE FILED: Apr. 8, 1994  
ART-UNIT: 182  
PRIM-EXMR: Stephen G. Walsh  
ASST-EXMR: Elizabeth C. Kemmerer  
LEGAL-REP: Townsend and Townsend and Crew

US PAT NO: 5,635,599 [IMAGE AVAILABLE] L3: 25 of 42

ABSTRACT:

The present invention provides for circularly permuted ligands which possess specificity and binding affinity comparable to or greater than the specificity and binding affinity of the original (unpermuted) ligand. The invention further provides for novel fusion proteins comprising a circularly permuted ligand fused to one or more proteins of interest.

US PAT NO: 5,629,315 [IMAGE AVAILABLE] L3: 26 of 42

DATE ISSUED: May 13, 1997

TITLE: Treatment of diseases using enantiomerically pure  
hydroxylated xanthine compounds

INVENTOR: James A. Bianco, Seattle, WA

Paul Woodson, Bothell, WA

David Porubek, Edmonds, WA

Jack Singer, Seattle, WA

ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)

APPL-NO: 08/456,900

DATE FILED: Jun. 1, 1995

ART-UNIT: 125

PRIM-EXMR: Theodore J. Criares

LEGAL-REP: Stephen Faciszewski

US PAT NO: 5,629,315 [IMAGE AVAILABLE] L3: 26 of 42

ABSTRACT:

There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

US PAT NO: 5,621,102 [IMAGE AVAILABLE] L3: 27 of 42

DATE ISSUED: Apr. 15, 1997

TITLE: Process for preparing enantiomerically pure xanthine  
derivatives

INVENTOR: James A. Bianco, Seattle, WA

Paul Woodson, Bothell, WA

David Porubek, Edmonds, WA

Jack Singer, Seattle, WA

ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)

APPL-NO: 08/456,897

DATE FILED: Jun. 1, 1995

ART-UNIT: 123

PRIM-EXMR: Alan L. Rotman

LEGAL-REP: Stephen Faciszewski

US PAT NO: 5,621,102 [IMAGE AVAILABLE] L3: 27 of 42

ABSTRACT:

There is disclosed compounds and pharmaceutical compositions that are a

resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in effective amounts.

US PAT NO: 5,620,984 [IMAGE AVAILABLE] L3: 28 of 42

DATE ISSUED: Apr. 15, 1997

TITLE: Enantiomerically pure hydroxylated xanthine compounds to treat inflammatory diseases

INVENTOR: James A. Bianco, Seattle, WA

Paul Woodson, Bothell, WA

David Porubek, Edmonds, WA

Jack Singer, Seattle, WA

ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)

APPL-NO: 08/456,898

DATE FILED: Jun. 1, 1995

ART-UNIT: 125

PRIM-EXMR: Theodore J. Criares

LEGAL-REP: Stephen Faciszewski, Jeffrey B. Oster

US PAT NO: 5,620,984 [IMAGE AVAILABLE] L3: 28 of 42

ABSTRACT:

There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in treating inflammatory disease.

US PAT NO: 5,614,642 [IMAGE AVAILABLE] L3: 29 of 42

DATE ISSUED: Mar. 25, 1997

TITLE: Methods of inhibiting phosphatase activity and treatment of disorders associated therewith using naphthopyrones and derivatives thereof

INVENTOR: Peng C. Tang, Moraga, CA

Gerald McMahon, Kenwood, CA

ASSIGNEE: Sugan Inc., Redwood City, CA (U.S. corp.)

APPL-NO: 08/599,453

DATE FILED: Jan. 22, 1996

ART-UNIT: 121

PRIM-EXMR: Johann Richter

ASST-EXMR: Laura R. Cross

LEGAL-REP: Pennie & Edmonds

US PAT NO: 5,614,642 [IMAGE AVAILABLE] L3: 29 of 42

ABSTRACT:

The present invention relates to organic molecules capable of inhibiting protein tyrosine phosphatase activity. The invention further relates to the use of such molecules to modulate or regulate signal transduction by inhibiting protein tyrosine phosphatase activity. Finally, the invention



relates to the use of such molecules to treat various disease states including diabetes mellitus.

US PAT NO: 5,614,191 [IMAGE AVAILABLE] L3: 30 of 42  
DATE ISSUED: Mar. 25, 1997  
TITLE: IL-13 receptor specific chimeric proteins and uses thereof  
INVENTOR: Raj K. Puri, North Potomac, MD  
Waldemar Debinski, Hummelstown, PA  
Ira Pastan, Potomac, MD  
Nicholas Obiri, Gaithersburg, MD  
ASSIGNEE: The United States of America as represented by the  
Department of Health and Human Services, Washington, DC  
(U.S. govt.)  
APPL-NO: 08/404,685  
DATE FILED: Mar. 15, 1995  
ART-UNIT: 183  
PRIM-EXMR: Christine M. Nucker  
ASST-EXMR: Julie E. Reeves  
LEGAL-REP: Townsend and Townsend and Crew LLP

US PAT NO: 5,614,191 [IMAGE AVAILABLE] L3: 30 of 42

ABSTRACT:

The present invention provides a method and compositions for specifically delivering an effector molecule to a tumor cell. The method involves providing a chimeric molecule that comprises an effector molecule attached to a targeting molecule that specifically binds an IL-13 receptor and contacting a tumor cell with the chimeric molecule.

US PAT NO: 5,612,349 [IMAGE AVAILABLE] L3: 31 of 42  
DATE ISSUED: Mar. 18, 1997  
TITLE: Enantiomerically pure hydroxylated xanthine compounds to treat shock symptoms  
INVENTOR: James A. Bianco, Seattle, WA  
Paul Woodson, Bothell, WA  
David Porubek, Edmonds, WA  
Jack Singer, Seattle, WA  
ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)  
APPL-NO: 08/457,062  
DATE FILED: Jun. 1, 1995  
ART-UNIT: 125  
PRIM-EXMR: Theodore J. Criares  
LEGAL-REP: Stephen Faciszewski

US PAT NO: 5,612,349 [IMAGE AVAILABLE] L3: 31 of 42

ABSTRACT:

There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in modulating cellular response to external or in situ primary stimuli, as well as to specific modes of administration of such compounds in

effective amounts.

US PAT NO: 5,612,185 [IMAGE AVAILABLE] L3: 32 of 42  
DATE ISSUED: Mar. 18, 1997  
TITLE: Method for identifying tumor cells in cell cycle arrest  
INVENTOR: Jonathan W. Uhr, Dallas, TX  
Ellen S. Vitetta, Dallas, TX  
Louis J. Picker, Dallas, TX  
Richard H. Scheuermann, Carrollton, TX  
ASSIGNEE: Board of Regents, The University of Texas System, Austin,  
TX (U.S. corp.)  
APPL-NO: 08/306,525  
DATE FILED: Sep. 15, 1994  
ART-UNIT: 182  
PRIM-EXMR: James C. Housel  
ASST-EXMR: Gary Tanigawa  
LEGAL-REP: Arnold, White & Durkee

US PAT NO: 5,612,185 [IMAGE AVAILABLE] L3: 32 of 42

ABSTRACT:

Disclosed are methods for the identification and characterization of tumor cell types present within malignant populations, and novel methods of cancer treatment. Tumor cells in cell cycle arrest have been identified, purified and characterized according to their size, altered morphology, surface phenotype and expression of oncogenes. Tumor cell cycle arrest can be induced in mice lacking an immune system solely upon administration of anti-idiotypic \*\*antibodies\*\*. Methods of manipulating specific signals from the cell surface to alter the malignant phenotype of transformed cells are disclosed, as are methods for either eliminating or specifically maintaining tumor cells in cell cycle arrest.

US PAT NO: 5,602,171 [IMAGE AVAILABLE] L3: 33 of 42  
DATE ISSUED: Feb. 11, 1997  
TITLE: Methods of inhibiting phosphatase activity and treatment  
of disorders associated therewith using naphthopyrones  
and derivatives thereof  
INVENTOR: Peng C. Tang, Moraga, CA  
Gerald McMahon, Kenwood, CA  
ASSIGNEE: Sugen Inc., Redwood City, CA (U.S. corp.)  
APPL-NO: 08/481,955  
DATE FILED: Jun. 7, 1995  
ART-UNIT: 121  
PRIM-EXMR: Johann Richter  
ASST-EXMR: Laura R. Cross  
LEGAL-REP: Pennie & Edmonds

US PAT NO: 5,602,171 [IMAGE AVAILABLE] L3: 33 of 42

ABSTRACT:

The present invention relates to organic molecules capable of inhibiting protein tyrosine phosphatase activity. The invention further relates to the use of such molecules to modulate or regulate signal transduction by

inhibiting protein tyrosine phosphatase activity. Finally, the invention relates to the use of such molecules to treat various disease states including diabetes mellitus.

US PAT NO: 5,602,095 [IMAGE AVAILABLE] L3: 34 of 42  
DATE ISSUED: Feb. 11, 1997  
TITLE: Recombinant pseudomonas exotoxin with increased activity  
INVENTOR: Ira H. Pastan, Potomac, MD  
David J. Fitzgerald, Silver Springs, MD  
ASSIGNEE: The United States of America as represented by the  
Secretary of the Department of Health and Human Services  
, Washington, DC (U.S. govt.)  
APPL-NO: 08/405,615  
DATE FILED: Mar. 15, 1995  
ART-UNIT: 184  
PRIM-EXMR: Christopher S. F. Low  
LEGAL-REP: Townsend and Townsend and Crew LLP

US PAT NO: 5,602,095 [IMAGE AVAILABLE] L3: 34 of 42

ABSTRACT:

This invention relates to the production and use of recombinant Pseudomonas-derived toxins modified to increase their toxicity and potency in therapy. More particularly, the invention relates to certain deletions in domain II of the amino acid sequence of Pseudomonas exotoxin the domain which relates to the toxin's natural proteolytic processing.

US PAT NO: 5,580,874 [IMAGE AVAILABLE] L3: 35 of 42  
DATE ISSUED: Dec. 3, 1996  
TITLE: Enantiomerically pure hydroxylated xanthine compounds  
INVENTOR: James A. Bianco, Seattle, WA  
Paul Woodson, Bothell, WA  
David Porubek, Edmonds, WA  
Jack Singer, Seattle, WA  
ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)  
APPL-NO: 08/457,685  
DATE FILED: Jun. 1, 1995  
ART-UNIT: 125  
PRIM-EXMR: Theodore J. Criares  
LEGAL-REP: Stephen Faciszewski

US PAT NO: 5,580,874 [IMAGE AVAILABLE] L3: 35 of 42

ABSTRACT:

There is disclosed compounds and pharmaceutical compositions that is R enantiomer of an  $\omega$ -1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in treating the side effects of immunosuppressive agent and interleukin-2 therapy.

US PAT NO: 5,580,873 [IMAGE AVAILABLE] L3: 36 of 42  
DATE ISSUED: Dec. 3, 1996

TITLE: Enantiomerically pure hydroxylated xanthine compounds to  
treat proliferative vascular diseases

INVENTOR: James A. Bianco, Seattle, WA  
Paul Woodson, Bothell, WA  
David Porubek, Edmonds, WA  
Jack Singer, Seattle, WA

ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)

APPL-NO: 08/456,899

DATE FILED: Jun. 1, 1995

ART-UNIT: 125

PRIM-EXMR: Theodore J. Criares

LEGAL-REP: Jeffrey B. Oster

US PAT NO: 5,580,873 [IMAGE AVAILABLE] L3: 36 of 42

ABSTRACT:

There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in treating proliferative vascular disease.

US PAT NO: 5,567,704 [IMAGE AVAILABLE] L3: 37 of 42

DATE ISSUED: Oct. 22, 1996

TITLE: R-enantiomerically pure hydroxylated xanthine compounds to  
treat baldness

INVENTOR: James A. Bianco, Seattle, WA  
Paul Woodson, Bothell, WA  
David Porubek, Edmonds, WA  
Jack Singer, Seattle, WA

ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)

APPL-NO: 08/457,683

DATE FILED: Jun. 1, 1995

ART-UNIT: 125

PRIM-EXMR: Theodore J. Criares

LEGAL-REP: Jeffrey B. Oster

US PAT NO: 5,567,704 [IMAGE AVAILABLE] L3: 37 of 42

ABSTRACT:

There is disclosed compounds and pharmaceutical compositions that are a resolved R or S (preferably R) enantiomer of an .omega.-1 alcohol of a straight chain alkyl (C.sub.5-8) substituted at the 1-position of 3,7-disubstituted xanthine. The inventive compounds are effective in treating baldness.

US PAT NO: 5,529,925 [IMAGE AVAILABLE] L3: 38 of 42

DATE ISSUED: Jun. 25, 1996

TITLE: Nucleic acid sequences and fusion proteins present in  
human t(2;5) lymphoma

INVENTOR: Stephan W. Morris, Memphis, TN  
A. Thomas Look, Memphis, TN

ASSIGNEE: St. Jude Children's Research Hospital, Memphis, TN (U.S.

corp.)

APPL-NO: 08/160,861  
DATE FILED: Dec. 3, 1993  
ART-UNIT: 184  
PRIM-EXMR: Charles L. Patterson, Jr.  
ASST-EXMR: Keith D. Hendricks  
LEGAL-REP: Sterne, Kessler, Goldstein & Fox

US PAT NO: 5,529,925 [IMAGE AVAILABLE] L3: 38 of 42

ABSTRACT:

The present invention is based on the identification and sequence determination of fusion proteins generated by translocation which is present in t(2;5) lymphoma cells. Using either the amino acid or nucleic acid sequences of the fusion proteins disclosed herein, the present invention provides methods of detecting and treating t(2;5) lymphoma.

US PAT NO: 5,521,315 [IMAGE AVAILABLE] L3: 39 of 42

DATE ISSUED: May 28, 1996

TITLE: Olefin substituted long chain compounds

INVENTOR: Gail Underiner, Brier, WA

David Porubek, Seattle, WA

J. Peter Klein, Vashon, WA

Elisa Eiseman, Seattle, WA

Alistair Leigh, Brier, WA

Anil Kumar, Seattle, WA

John Michnick, Seattle, WA

ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)

APPL-NO: 08/059,697

DATE FILED: May 10, 1993

ART-UNIT: 122

PRIM-EXMR: Mukund J. Shah

ASST-EXMR: Pavanaram K. Sripada

LEGAL-REP: Stephen Faciszewski, Jeffrey B. Oster

US PAT NO: 5,521,315 [IMAGE AVAILABLE] L3: 39 of 42

ABSTRACT:

There is disclosed an olefin-substituted compound having the formula:

R--(core moiety),

wherein R is a straight chain hydrocarbon having at least one double bond and a carbon chain length of from about 6 to about 18 carbon atoms, wherein multiple double bonds are separated from each other by at least three carbon atoms, wherein the closest double bond to the core moiety is at least five carbon atoms from the core moiety, and wherein the hydrocarbon chain may be substituted by a hydroxyl, halo, keto or dimethylanimo group and/or interrupted by an oxygen atom and salts thereof and pharmaceutical compositions thereof.

US PAT NO: 5,521,295 [IMAGE AVAILABLE] L3: 40 of 42

DATE ISSUED: May 28, 1996

TITLE: Nucleic acids encoding hybrid receptor molecules

INVENTOR: Robert E. Pacifici, Thousand Oaks, CA  
Arlen R. Thomason, Thousand Oaks, CA  
ASSIGNEE: Amgen Inc., Thousand Oaks, CA (U.S. corp.)  
APPL-NO: 08/336,708  
DATE FILED: Nov. 8, 1994  
ART-UNIT: 187  
PRIM-EXMR: W. Gary Jones  
ASST-EXMR: David Schreiber  
LEGAL-REP: Nancy Oleski

US PAT NO: 5,521,295 [IMAGE AVAILABLE] L3: 40 of 42

ABSTRACT:

Provided are hybrid receptor molecules wherein one domain of the receptor is derived from the cytokine superfamily of receptors and other domain is derived from a heterologous family of receptors. Also provided are methods for identifying ligands that bind to the hybrid receptor molecules.

US PAT NO: 5,470,878 [IMAGE AVAILABLE] L3: 41 of 42  
DATE ISSUED: Nov. 28, 1995  
TITLE: Cell signaling inhibitors  
INVENTOR: John Michnick, Seattle, WA  
Gail E. Underiner, Brier, WA  
J. Peter Klein, Vashon Island, WA  
Glenn C. Rice, Seattle, WA  
ASSIGNEE: Cell Therapeutics, Inc., Seattle, WA (U.S. corp.)  
APPL-NO: 08/164,081  
DATE FILED: Dec. 8, 1993  
ART-UNIT: 129  
PRIM-EXMR: Shailendra Kumar  
LEGAL-REP: Stephen Faciszewski, Jeffrey B. Oster

US PAT NO: 5,470,878 [IMAGE AVAILABLE] L3: 41 of 42

ABSTRACT:

Therapeutic compounds have the formula:

(X)<sub>j</sub>-(non-cyclic core moiety),  
j being an integer from one to three, the core moiety is non-cyclic and X is a racemic mixture, R or S enantiomer, solvate, hydrate, or salt of:  
##STR1## \*C is a chiral carbon atom, n is an integer from one to four (preferably from one to three), one or more carbon atoms of (CH.sub.2).sub.n may be substituted by a keto or hydroxy group, and m is an integer from one to fourteen. Independently, R.sub.1 and R.sub.2 may be a hydrogen, a straight or branched chain alkane or alkene of up to twelve carbon atoms in length, or --(CH.sub.2).sub.w R.sub.5, w being an integer from two to fourteen and R.sub.5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R.sub.5 being hydroxy, chloro, fluoro, bromo, or C.sub.1-6 alkoxy. Or jointly, R.sub.1 and R.sub.2 form a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon atoms, N being a hetero atom. R.sub.3 is a hydrogen or C.sub.1-3. Or, therapeutic compounds may also have the formula: ##STR2## R.sub.4 is a hydrogen, a

straight or branched chain alkane or alkene of up to eight carbon atoms in length, --(CH.sub.2).sub.w R.sub.5, w being an integer from two to fourteen and R.sub.5 being a mono-, di- or tri-substituted or unsubstituted aryl group, substituents on R.sub.5 being hydroxy, chloro, fluoro, bromo, or C.sub.1-6 alkoxy, or a substituted or unsubstituted, saturated or unsaturated heterocyclic group having from four to eight carbon atoms. r and s are independently integers from one to four, the sum (r+s) not being greater than five. t is an integer from one to fourteen and one or more carbon atoms of (CH.sub.2).sub.s or (CH.sub.2).sub.t may be substituted by a keto or hydroxy group.

US PAT NO: 5,367,060 [IMAGE AVAILABLE] L3: 42 of 42  
DATE ISSUED: Nov. 22, 1994  
TITLE: Structure, production and use of heregulin  
INVENTOR: Richard L. Vandlen, Hillsborough, CA  
William E. Holmes, Pacifica, CA  
ASSIGNEE: Genentech, Inc., So. San Francisco, CA (U.S. corp.)  
APPL-NO: 07/847,743  
DATE FILED: Mar. 6, 1992  
ART-UNIT: 182  
PRIM-EXMR: Robert J. Hill, Jr.  
ASST-EXMR: K. Cochrane Carlson  
LEGAL-REP: Wendy M. Lee

US PAT NO: 5,367,060 [IMAGE AVAILABLE] L3: 42 of 42

ABSTRACT:

A novel polypeptide with binding affinity for the p185.sup.\*\*HER2\*\* receptor, designated heregulin-.alpha., has been identified and purified from cultured human cells. DNA sequences encoding additional heregulin polypeptides, designated heregulin-.alpha., heregulin-.beta.1, heregulin-.beta.2, heregulin-.beta.2-like, and heregulin-.beta.3, have been isolated, sequenced and expressed. Provided herein are nucleic acid sequences encoding the amino acid sequences of heregulins useful in the production of heregulins by recombinant means. Further provided are the amino acid sequences of heregulins and purification methods therefor. Heregulins and their \*\*antibodies\*\* are useful as therapeutic agents and in diagnostic methods.

\*\*\*\*\*STN Columbus\*\*\*\*\*

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=> e fendly brian m/au

E1 1 FENDLY BRAIN M/AU

E2 13 FENDLY BRIAN/AU

E3 36 --> FENDLY BRIAN M/AU

E4 1 FENDON DAVID E/AU

E5 1 FENDORE S E/AU

E6 2 FENDORF K/AU

E7 29 FENDORF M/AU

E8 1 FENDORF M J/AU

E9 12 FENDORF MARK/AU

E10 1 FENDORF MARK J/AU

E11 1 FENDORF MARK JOHN/AU

E12 12 FENDORF S/AU

=> s e1-e3

L1 50 ("FENDLY BRAIN M"/AU OR "FENDLY BRIAN"/AU OR "FENDLY BRIAN M"/AU)

=> dup rem l1

PROCESSING COMPLETED FOR L1

L2 50 DUP REM L1 (0 DUPLICATES REMOVED)

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L2 ANSWER 1 OF 50 CAPLUS COPYRIGHT 1998 ACS

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DN 128:307524

TI Antibodies to the neu receptor capable of inducing apoptosis and their therapeutic uses

IN \*\*\*Fendly, Brian M.\*\*\* ; Phillips, Gail Dianne; Scheuermann, Richard H.; Uhr, Jonathan W.

PA Genentech, Inc., USA; Board of Regents, the University of Texas System

SO PCT Int. Appl., 77 pp.

CODEN: PIXXD2

PI WO 9817797 A1 19980430

DS W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG

AI WO 97-US18385 19971009

PRAI US 96-731794 19961018

DT Patent

LA English

AB Anti-ErbB2 antibodies that bind to an epitope in Domain 1 of the receptor (the neu receptor) and induce cell death via apoptosis are described. These antibodies have a no. of uses, e.g. in the treatment of ovarian cancer and in detection of overexpression of the erbB2 gene.

L2 ANSWER 2 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1997:556436 CAPLUS



DN 127:243337

TI Mutational analysis of thrombopoietin for identification of receptor and neutralizing antibody sites

AU Pearce, Kenneth H., Jr.; Potts, Beverly J.; Presta, Leonard G.; Bald, Laura N.; \*\*\*Fendly, Brian M.\*\*\* ; Wells, James A.

CS Departments of Protein Engineering, South San Francisco, CA, 94080, USA

SO J. Biol. Chem. (1997), 272(33), 20595-20602

CODEN: JBCHA3; ISSN: 0021-9258

PB American Society for Biochemistry and Molecular Biology

DT Journal

LA English

AB Thrombopoietin (TPO) is a hematopoietin important for megakaryocyte proliferation and prodn. of blood platelets. We sought to characterize how TPO binds and activates its receptor, myeloproliferative leukemia virus receptor. The erythropoietin-like domain of TPO (TPO1-153) has been fused to the gIII coat protein of M13 bacteriophage. Forty residues were chosen for mutation to alanine using the criteria that they were charged residues or predicted to be solvent-exposed, based on a homol. model. Phage ELISA was used to det. affinities for binding to both the TPO receptor and five anti-TPO1-15e monoclonal antibodies. Mutations at mostly pos. charged residues (Asp8, Lys14, Lys52, Lys59, Lys136, Lys138, Arg140) caused the greatest redn. in receptor-binding affinity. Most of these residues mapped to helices-1 and -4 and a loop region between helix-1 and helix-2. Two of the monoclonal antibodies that blocked TPO binding and bioactivity had determinants in helix-4. In contrast, the other three monoclonal antibodies, which were effective at blocking TPO activity but did not block initial binding of TPO to its receptor, had epitopes predominantly on helix or 3. These results suggest that TPO has two distinct receptor-binding sites that function to dimerize TPO receptors in a sequential fashion.

L2 ANSWER 3 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1998:9254 CAPLUS

DN 128:73592

TI Neutralizing antibodies against epidermal growth factor and ErbB-2/neu receptor tyrosine kinases down-regulate vascular endothelial growth factor production by tumor cells in vitro and in vivo: angiogenic implications for signal transduction therapy of solid tumors

AU Petit, Alicia M. Vilorio; Rak, Janusz; Hung, Mien-Chie; Rockwell, Patricia; Goldstein, Neil; \*\*\*Fendly, Brian\*\*\* ; Kerbel, Robert S.

CS Division of Cancer Biology Research, Sunnybrook Health Science Centre, Department of Biophysics, Univ. of Toronto, Toronto, ON, Can.

SO Am. J. Pathol. (1997), 151(6), 1523-1530

CODEN: AJPA44; ISSN: 0002-9440

PB American Society for Investigative Pathology

DT Journal

LA English

AB The overexpression in tumor cells of (proto)-oncogenic receptor tyrosine kinases such as epidermal growth factor receptor (EGFR) or

ErbB2/neu (also known as HER-2) is generally thought to contribute to the development of solid tumors primarily through their effects on promoting uncontrolled cell proliferation. However, agents that antagonize the function of the protein products encoded by these (proto)-oncogenes are known to behave *in vivo* in a cytotoxic-like manner. This implies that such oncogenes may regulate crit. cell survival functions, including angiogenesis. The latter could occur as a consequence of regulation of relevant growth factors by such oncogenes. The authors therefore sought to det. whether EGFR or ErbB2/neu may contribute to tumor angiogenesis by examg. their effects on the expression of vascular endothelial cell growth factor (VEGF)/vascular permeability factor (VPF), one of the most important of all known inducers of tumor angiogenesis. The authors found that *in vitro* treatment of EGFR-pos. A431 human epidermoid carcinoma cells, which are known to be heavily dependent on VEGF/VPF *in vivo* as an angiogenesis growth factor, with the C225 anti-EGFR neutralizing antibody caused a dose-dependent inhibition of VEGF protein expression. Prominent suppression of VEGF/VPF expression *in vivo*, as well as a significant redn. in tumor blood vessel counts, were also obsd. in established A431 tumors shortly after injection of the antibody as few as four times into nude mice. Transformation of NIH 3T3 fibroblasts with mutant ErbB2/neu, another EGFR-like oncogenic tyrosine kinase, resulted in a significant induction of VEGF/VPF, and the magnitude of this effect was further elevated by hypoxia. Moreover, treatment of ErbB2/neu-pos. SKBR-3 human breast cancer cells *in vitro* with a specific neutralizing anti-ErbB2/neu monoclonal antibody (4D5) resulted in a dose-dependent redn. of VEGF/VPF protein expression. Taken together, the results suggest that oncogenic properties of EGFR and ErbB2/neu may, at least in part, be mediated by stimulation of tumor angiogenesis by up-regulating potent angiogenesis growth factors such as VEGF/VPF. These genetic changes may cooperate with epigenetic/environmental effects such as hypoxia to maximally stimulate VEGF/VPF expression. Therapeutic disruption of EGFR or ErbB2/neu protein function *in vivo* may therefore result in partial suppression of angiogenesis, a feature that could enhance the therapeutic index of such agents *in vivo* and endow them with anti-tumor effects, the magnitude of which may be out of proportion with their obsd. cytostatic effects in monolayer tissue culture.

L2 ANSWER 4 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1996:155468 CAPLUS

DN 124:257028

TI Growth regulations of human breast and ovarian tumor cells by heregulin: evidence for the requirement of ErbB2 as a critical component in mediating heregulin responsiveness

AU Lewis, Gail D.; Lofgren, Julie A.; McMurtrey, Amy E.; Nuijens, Andrew; \*\*\*Fendly, Brian M.\*\*\* ; Bauer, Kenneth D.; Slivkowski, Mark X.

CS Genentech, Inc., South San Francisco, CA, 94080, USA

SO Cancer Res. (1996), 56(6), 1457-65

CODEN: CNREA8; ISSN: 0008-5472

DT Journal

LA English

AB Alterations in the expression of the epidermal growth factor (EGF)

receptor ErbB family are frequently encountered in a no. of human cancers. Two of these receptors, ErbB3 and ErbB4, are known to bind a family of related proteins termed heregulins (HRGs) or neu differentiation factors. In biol. relevant systems, interaction of HRG with ErbB3 or ErbB4 results in the transactivation of ErbB2. In this report, the authors show that ErbB2 is a crit. component in mediating HRG responsiveness in a panel of human breast and ovarian tumor cell lines. Because HRGs have been reported to elicit diverse biol. effects on cultured cells, including growth stimulation, growth inhibition, and induction of differentiation, the authors systematically examd. the effect of rHRG.beta.1 on tumor cell proliferation. HRG binding studies were performed with a panel of breast and ovarian tumor cell lines expressing a range of levels of ErbB2. The biol. response to HRG were also compared to EGF and to the growth-inhibitory anti-ErbB2 antibody, 4D5. In most cases, HRG stimulation of DNA synthesis correlated with pos. effects on cell cycle progression and cell no. and with enhancement of colony formation in soft agar. On each cell line tested, the HRG effects were distinguishable from EGF and 4D5. These findings indicate that HRG induces cell proliferation in a no. of tumor cell lines. In addn., the authors show that methods for measuring cell proliferation, as well as exptl. conditions, are crit. for detg. HRGs effect on tumor cell growth in vitro.

L2 ANSWER 5 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1995:410223 CAPLUS

DN 122:179262

TI Natriuretic peptide receptor-B (guanylyl cyclase-B) mediates C-type natriuretic peptide relaxation of precontracted rat aorta

AU Drewett, James G.; \*\*\*Fendly, Brian M.\*\*\* ; Garbers, David L.; Lowe, David G.

CS Department of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee, WI, 53226, USA

SO J. Biol. Chem. (1995), 270(9), 4668-74

CODEN: JBCHA3; ISSN: 0021-9258

DT Journal

LA English

AB The most potent known agonist for the natriuretic peptide receptor-B (NPR-B)/guanylyl cyclase-B is C-type natriuretic peptide (CNP). A homologous ligand-receptor system consists of atrial natriuretic peptide (ANP) and NPR-A/guanylyl cyclase-A. A third member of this family is NPR-C, a non-guanylyl cyclase receptor. Monoclonal antibodies were raised against NPR-B by immunizing mice with a purified receptor-IgG fusion protein consisting of the extracellular domain of NPR-B and the Fc portion of human IgG-.gamma.1. One monoclonal antibody, 3G12, did not recognize NPR-A or NPR-C and bound to human and rat NPR-B. CNP binding to NPR-B and stimulation of cGMP synthesis were inhibited by 3G12. With cells isolated from either the media or adventitia layers of rat thoracic aorta, 3G12 did not interfere with ANP-stimulated cGMP synthesis, but it inhibited CNP-stimulated cGMP levels in cells from both layers. CNP (IC50 = 10 nM) and ANP (IC50 = 1 nM) caused relaxation of phenylephrine-contracted rat aortic rings. 3G12 caused a marked increase in the IC50 for CNP, from 10 nM to 140 nM, but failed to affect ANP-mediated relaxation. Therefore, the results for the

first time demonstrate that CNP relaxes vascular smooth muscle by virtue of its binding to NPR-B.

L2 ANSWER 6 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1995:444899 CAPLUS

DN 123:163923

TI Molecular cloning of a ligand for the EPH-related receptor protein-tyrosine kinase Htk

AU Bennett, Brian D.; Ziegler, Francis C.; Gu, Qimin; \*\*\*\*Fendly,\*\*\*  
\*\*\* Brian\*\*\* ; Goddard, Audrey D.; Gillett, Nancy; Matthews, William  
CS Dep. Molecular Biology Hybridoma, Genentech, Inc., South San  
Francisco, CA, 94080, USA

SO Proc. Natl. Acad. Sci. U. S. A. (1995), 92(6), 1866-70

CODEN: PNASA6; ISSN: 0027-8424

DT Journal

LA English

AB Htk is a receptor protein-tyrosine kinase that is related to the EPH subfamily of tyrosine kinases. The receptor has a wide tissue distribution including expression in several myeloid hematopoietic cell lines. Using an Htk-Fc fusion protein, a protein ligand for this receptor was expression cloned from the murine kidney mesangial cell line SV40MES 13. The Htk ligand cDNA encodes a transmembrane protein of 336 amino acids. Binding competition expts. demonstrated a Kd of 535 pM for binding of Htk-Fc to the Htk ligand. Incubation of 3T3 cells expressing Htk with COS-7 cells expressing the ligand resulted in tyrosine phosphorylation of Htk. The ligand, like its receptor, is widely expressed and may function in a variety of tissues. However, hematopoietic expression of Htk was localized to the monocytic lineage, suggesting that the ligand may play a role in differentiation and/or proliferation of these cells.

L2 ANSWER 7 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1995:748330 CAPLUS

DN 123:225803

TI Inhibition of allergic reactions with antibodies in IgE

AU Shields, Robert L.; Whether, Winifred R.; Zioncheck, Kimberly;  
O'Connell, Lori; \*\*\*\*Fendly, Brian\*\*\* ; Presta, Leonard G.;  
Thomas, Deborah; Saban, Ricardo; Jardieu, Paula

CS Sch. Vet. Med., Univ. Wisconsin, Madison, WI, USA

SO Int. Arch. Allergy Immunol. (1995), 107(1-3), 308-12

CODEN: IAAIEG; ISSN: 1018-2438

DT Journal

LA English

AB Numerous clin. studies show that direct interference with the IgE response leads to a decrease or elimination of allergic symptoms. The aim of these studies was to design a therapy aimed at decreasing IgE levels to ameliorate atopic disease. To this end, a murine monoclonal antibody, MAE11, directed against IgE was identified, which had all the properties necessary to interfere with IgE responses, but lacked the harmful side effects of inducing receptor crosslinking. The antibody was selected on the basis of its ability to bind circulating IgE at the same site as the high-affinity receptor, thus blocking the binding of IgE to mast cells and basophils. To allow for possible chronic administration and to avoid the problems of antigenicity, MAE11 was humanized. The best

of several humanized variants, version 25 (rhum AB-E25) was selected since it possessed binding affinity and biol. activity comparable to MAE11. Clin. studies are underway to det. the safety and efficacy of this treatment for allergic rhinitis and asthma.

L2 ANSWER 8 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1995:709813 CAPLUS

DN 123:167138

TI Development and characterization of murine monoclonal antibodies to the latency-associated peptide of transforming growth factor .beta.1

AU Hongo, Jo-Anne S.; Mora-Worms, Marina; Lucas, Catherine;  
\*\*\*Fendly, Brian M.\*\*\*

CS Department Bioanalytical Technology, Genentech, Inc., South San Francisco, CA, 94080, USA

SO Hybridoma (1995), 14(3), 253-60

CODEN: HYBRDY; ISSN: 0272-457X

DT Journal

LA English

AB Transforming growth factor .beta. (TGF-.beta.) is a multifunctional peptide that controls proliferation, differentiation, and other functions in a variety of cell types. Transforming growth factor .beta. activities have been implicated in a variety of diseased states including arthritis, prostate cancer, and AIDS, and in the repair of tissue injury caused by trauma, burns, and surgery. We describe the development and characterization of novel murine monoclonal antibodies (MAbs) to the latency-assocd. peptide (LAP) of TGF-.beta.1, and the subsequent development of an ELISA for the detection and quantitation of TGF-.beta.1-LAP in buffer and serum matrixes. Fusion of immune splenocytes with myeloma cells yielded 576 hybridomas, 110 of which were antibody secreting. Five were selected for extensive characterization. Clin., the MAbs described here should be valuable for studying potentially abnormal prodn. and/or function of the LAP, and its relationship to TGF-.beta..

L2 ANSWER 9 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1994:433162 CAPLUS

DN 121:33162

TI Monoclonal antibodies against type 2 tumor necrosis factor receptor (TNF-R2)

IN \*\*\*Fendly, Brian\*\*\* ; Goeddel, David V.; Palladino, Michael A.; Tartaglia, Louis A.

PA Genentech, Inc., USA

SO PCT Int. Appl., 42 pp.

CODEN: PIXXD2

PI WO 9409137 A1 19940428

DS W: CA, JP

RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

AI WO 93-US9620 19931008

PRAI US 92-961602 19921015

DT Patent

LA English

AB Monoclonal anti-TNF-R2 antibodies which mimic the T-cell proliferation stimulating activity of TNF are disclosed for treating patients with malignant tumor, T-cell mediated autoimmune disorders, immunodeficiencies, HIV, graft-vs.-host disease, and potential of

allograft rejection. Bispecific antibodies specific for TNF-R2 and for a T-cell surface protein (e.g. CD antigen, interleukin-2 receptor, or GD3 ganglioside), and gene therapy by using retroviral vector for introducing gene encoding said monoclonal antibody and gene for adenine deaminase, purine nucleoside phosphorylase, or hypoxanthine-guanine phosphoribosyltransferase are also claimed.

L2 ANSWER 10 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1994:401903 CAPLUS

DN 121:1903

TI Coexpression of erbB2 and erbB3 proteins reconstitutes a high affinity receptor for heregulin

AU Sliwkowski, Mark X.; Schaefer, Gabriele; Akita, Robert W.; Lofgren, Julie A.; Fitzpatrick, V. Danial; Nuijens, Andrew; \*\*\*Fendly,\*\*\*

\*\*\* Brian M.\*\*\* ; Cerione, Richard A.; Vandlen, Richard L.; Carraway, Kermit L., III

CS Genentech, Inc., South San Francisco, CA, 94080, USA

SO J. Biol. Chem. (1994), 269(20), 14661-5

CODEN: JBCHA3; ISSN: 0021-9258

DT Journal

LA English

AB The heregulin/neu differentiation factor gene products were purified and cloned based on their ability to stimulate the phosphorylation of a 185-kDa protein in human breast carcinoma cell lines known to express erbB2. However, not all cells that express erbB2 respond to heregulin, indicating that other components besides erbB2 may be required for heregulin binding. Cells that are transfected with the closely related receptor, erbB3, display a single class of lower affinity heregulin binding sites than has been previously obsd. on breast carcinom cell lines. Little or no stimulation of tyrosine phosphorylation in response to heregulin occurs in cells that are transfected with erbB3 alone. Transfection of cells with erbB3 and erbB2 reconstitutes a higher affinity binding receptor, which is also capable of generating a tyrosine phosphorylation signal in response to heregulin. A monoclonal antibody to erbB2 will inhibit heregulin activation of tyrosine phosphorylation and binding in cells transfected with both receptors but not with erbB3 alone. In cells expressing erbB2 and erbB3, both proteins become tyrosine-phosphorylated upon interaction with heregulin. Direct interaction between heregulin and the two proteins was demonstrated by chem. crosslinking expts. using 125I-heregulin followed by immunopptn. with antibodies specific for erbB2 and erbB3.

L2 ANSWER 11 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1995:244754 CAPLUS

DN 122:7696

TI Activation of TNF-R1 receptors in the presence of copper kills TNF resistant CEM leukemic T cells

AU Wada, H. Garrett; Fok, Katherine S.; \*\*\*Fendly, Brian M.\*\*\* ; Chiang, Nancy Y.; Sussman, Howard H.

CS Mol. Dev. Corp., Sunnyvale, CA, 94089, USA

SO J. Cell. Physiol. (1994), 161(3), 597-605

CODEN: JCLLAX; ISSN: 0021-9541

DT Journal

LA English

AB The cytotoxic effects of TNF on malignant cells are known to be mediated through high affinity surface receptors. The precise mechanism by which transformed cells are selectively killed by the activation of these receptors is yet unknown, but several intracellular signaling pathways are known to be involved. Phospholipase A2 activation by TNF-.alpha. has been shown to be important in the transduction of signals leading to cell death. The authors used monitoring of extracellular acidification rate as a measure of cellular metab. to follow the early time course of TNF effects on a human leukemic T cell line (CEM-SS cells). CEM-SS cells were relatively resistant to TNF cell killing but TNF caused an early stimulation of metab. within 2-4 h, followed by a suppression of metabolic activity occurring over 20 h. In contrast, a TNF sensitive subclone of CEM cells (C1Ca) showed a rapid and dramatic decrease in metabolic activity corresponding to cytotoxicity within 18 h. It was discovered that cupric o-phenanthroline markedly potentiated the effects of TNF on the resistant CEM-SS cells leading to cell death. This observation was specific for copper because ferric o-phenanthroline was without effect at the same concn. The copper cytotoxic effect was shown to be mediated through the TNF-R1 receptor and independent of phospholipase A2 signaling.

L2 ANSWER 12 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1993:668831 CAPLUS

DN 119:268831

TI Strain specificity and binding affinity requirements of neutralizing monoclonal antibodies to the C4 domain of gp120 from human immunodeficiency virus type 1

AU Nakamura, Gerald R.; Byrn, Randal; Wilkes, Denise M.; Fox, Judith A.; Hobbs, Maurine R.; Hastings, Richard; Wessling, Holly C.; Norcross, Michael A.; \*\*\*Fendly, Brian M.\*\*\* ; Berman, Phillip W.

CS Dep. Immunol., Genentech, Inc., South San Francisco, CA, 94080, USA

SO J. Virol. (1993), 67(10), 6179-91

CODEN: JOVIAM; ISSN: 0022-538X

DT Journal

LA English

AB The binding properties of seven CD4-blocking monoclonal antibodies raised against recombinant gp120 of human immunodeficiency virus type 1 strain MN (HIV-1MN) and two CD4-blocking monoclonal antibodies to recombinant envelope glycoproteins gp120 and gp160 of substrain IIIB of HIVLAI were analyzed. With a panel of recombinant gp120s from seven diverse HIV-1 isolates, eight of the nine antibodies were strain specific and one was broadly cross-reactive. Epitope mapping revealed that all nine antibodies bound to epitopes located in the fourth conserved domain (C4) of gp120. Within this region, three distinct epitopes could be identified: two were polymorphic between HIV-1 strains, and one was highly conserved. Studies with synthetic peptides demonstrated that the conserved epitope, recognized by antibody 13H8, was located between residues 431 and 439. Site-directed mutagenesis of gp120 demonstrated that residue 429 and/or 432 was crit. for the binding of the seven antibodies to gp120 from HIV-1MN. Similarly, residues 423 and 429 were essential for the binding of monoclonal antibody 5C2 raised against gp120 from HIV-1IIIB. The amino acids located at positions

423 and 429 were found to vary between strains of HIV-1 as well as between mol. clones derived from the MN and LAI isolates of HIV-1. Polymorphism at these positions prevented the binding of virus-neutralizing monoclonal antibodies and raised the possibility that HIV-1 neutralization serotypes may be defined on the basis of C4 domain sequences. Anal. of the binding characteristics of the CD4-blocking antibodies demonstrated that their virus-neutralizing activity was directly proportional to their gp120-binding affinity. These studies account for the strain specificity of antibodies to the C4 domain of gp120 and demonstrate for the first time that antibodies to this region can be as effective as those directed to the principal neutralizing determinant (V3 domain) in neutralizing HIV-1 infectivity.

L2 ANSWER 13 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1994:6561 CAPLUS

DN 120:6561

TI Stimulation of human T-cell proliferation by specific activation of the 75-kDa tumor necrosis factor receptor

AU Tartaglia, Louis A.; Goeddel, David V.; Reynolds, Carmen; Figari, Irene S.; Weber, Richard F.; \*\*\*\*Fendly, Brian M.\*\*\* ; Palladino, Michael A., Jr.

CS Dep. Mol. Biol., Genentech, Inc., South San Francisco, CA, 94080, USA

SO J. Immunol. (1993), 151(9), 4637-41

CODEN: JOIMA3; ISSN: 0022-1767

DT Journal

LA English

AB TNF-.alpha. can enhance the proliferation of human thymocytes stimulated by the comitogen Con A. To det. which of the two different TNF receptors is responsible for signaling this cellular response, the authors investigated the proliferation of human thymocytes in response to agonistic antibodies specific for the two TNF receptor types. In contrast to previously examd. TNF activities in human cells, thymocyte proliferation was stimulated in response to rabbit polyclonal antibodies directed against the 75-kDa TNF receptor (TNF-R2), but not those directed against the 55-kDa TNF receptor (TNF-R1). Lymphotoxin (TNF-.beta.) was also shown to stimulate human thymocyte proliferation, demonstrating that TNF-.beta. can initiate a biol. response that is mediated by TNF-R2. TNF-R2-mediated T-cell proliferation was not restricted to the immature T cells within the thymus, as the anti-TNF-R2 antibodies also stimulated the proliferation of peripheral T cells. As a first step toward identifying a specific agonist of TNF-R2 with therapeutic potential, 10 anti-TNF-R2 mAb were examd. for potential agonist activity. Nine of these significantly stimulated human thymocyte proliferation with maximal responses ranging from twofold to significantly greater than that obtained with TNF-.alpha. by itself.

L2 ANSWER 14 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1993:668528 CAPLUS

DN 119:268528

TI Humanization of an antibody directed against IgE

AU Presta, Leonard G.; Lahr, Steven J.; Shields, Robert L.; Porter,



James P.; Gorman, Cornelia M.; \*\*\*Fendly, Brian M.\*\*\* ; Jardieu, Paula M.

CS Dep. Protein Eng., Genentech, Inc., South San Francisco, CA, 94080, USA

SO J. Immunol. (1993), 151(5), 2623-32

CODEN: JOIMA3; ISSN: 0022-1767

DT Journal

LA English

AB IgE antibodies bind to specific high-affinity receptors on mast cells, leading to mast cell degranulation and release of mediators, such as histamine, which produce symptoms assocd. with allergy. Hence, anti-IgE antibodies that block binding of IgE to its high-affinity receptor are of potential therapeutic value in the treatment of allergy. These antibodies also must not bind to IgE once it is bound to the receptor because this would trigger histamine release. This study describes the humanization of a murine antibody, MaE11, with these characteristics. Variants of the humanized antibody were evaluated to probe the importance of framework residues on antibody binding and to det. which charged residues in the CDR interacted with IgE. Only five changes in human framework residues were required to provide for binding comparable to that of the original murine antibody.

L2 ANSWER 15 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1994:51443 CAPLUS

DN 120:51443

TI Anti-transforming growth factor (TGF)-.beta. antibodies inhibit breast cancer cell tumorigenicity and increase mouse spleen natural killer cell activity. Implications for a possible role of tumor cell/host TGF-.beta. interactions in human breast cancer progression

AU Arteaga, Carlos L.; Hurd, Stephen D.; Winnier, Angela R.; Johnson, Mahlon D.; \*\*\*Fendly, Brian M.\*\*\* ; Forbes, James T.

CS Sch. Med., Vanderbilt Univ., Nashville, TN, 37232, USA

SO J. Clin. Invest. (1993), 92(6), 2569-76

CODEN: JCINAO; ISSN: 0021-9738

DT Journal

LA English

AB TGF-.beta. effects on angiogenesis, stroma formation, and immune function suggest its possible involvement in tumor progression. This hypothesis was tested using the 2G7 IgG2b, which neutralizes TGF-.beta.1, -.beta.2, and -.beta.3, and the MDA-231 human breast cancer cell line. Inoculation of these cells in athymic mice decreases mouse spleen natural killer (NK) cell activity. I.p. injections of 2G7 starting 1 d after i.p. inoculation of tumor cells suppressed intraabdominal tumor and lung metastases, whereas the nonneutralizing anti-TGF-.beta. 12H5 IgG2a had no effect. 2G7 transiently inhibited growth of established MDA-231 s.c. tumors. Histol., both 2G7-treated and control tumors were identical. I.p. administration of 2G7 resulted in a marked increase in mouse spleen NK cell activity. 2G7 did not inhibit MDA-231 primary tumor on metastasis formation, nor did it stimulate NK cell-mediated cytotoxicity in beige NK-deficient nude mice. Finally, serum-free conditioned medium from MDA-231 cells inhibited the NK cell activity of human blood lymphocytes. This inhibition was blocked by the neutralizing anti-TGF-.beta. 2G7 antibody but not by a nonspecific

IgG2. These data support a possible role for tumor cell TGF- $\beta$  in the progression of mammary carcinomas by suppressing host immune surveillance.

L2 ANSWER 16 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1993:420634 CAPLUS

DN 119:20634

TI Development of a specific and sensitive two-site enzyme-linked immunosorbent assay for measurement of inhibin-A in serum

AU Baly, Deborah L.; Allison, David E.; Krummen, Lynne A.; Woodruff, Teresa K.; Soules, Michael R.; Chen, Sharon A.; \*\*\*Fendly, Brian\*\*\*

\*\*\* M\*\*\*; Bald, Laura N.; Mather, Jennie P.; Lucas, Catherine

CS Genentech, Inc., South San Francisco, CA, 94080, USA

SO Endocrinology (Baltimore) (1993), 132(5), 2099-108

CODEN: ENDOAO; ISSN: 0013-7227

DT Journal

LA English

AB A polyclonal chicken antiserum against purified 32-kilodalton (kDa) recombinant inhibin-A (rh-InhA) and 2 monoclonal antibodies (mAb) against either rh-InhA (11B5) or 28-kDa recombinant activin-A (rh-ActA; 9A9) were used to develop 3 sensitive InhA ELISAs. The sensitivity of an ELISA using affinity-purified chicken anti-rh-InhA (Ck) for both coat and capture (Ck/Ck) averaged 78 pg/mL, while the mAb/Ck ELISAs (11B5/Ck or 9A9/Ck) averaged 100 pg/mL in a 10% serum matrix, with intra- and interassay relative strd. deviations of 2-5 and 8-10%, resp., for all assays. The ELISA formats did not crossreact with purified rh-ActA or recombinant human transforming growth factor- $\beta$ 1 or detect any immunoreactive proteins in medium conditioned by cell lines expressing rh-ActA or recombinant human transforming growth factor- $\beta$ 1. The Ck/Ck ELISA detected significant amts. of immunoreactivity in medium from cells expressing the free  $\alpha$ -subunit of inhibin and recombinant inhibin-B (rh-InhB). In contrast, the mAb/Ck ELISAs showed no crossreactivity to medium conditioned by these 2 cell lines. All 3 ELISA formats detected rh-InhA added to either human or rat serum in vitro or serum from rats injected with rh-InhA. The Ck/Ck and 9A9/Ck ELISAs successfully quantitated inhibin in sera from patients undergoing ovulation induction and in rats (with or without s.c. administration of pregnant serum gonadotropin). The 11B5/Ck ELISA appeared to be specific for the 32-kDa form of inhibin, while the 9A9/Ck ELISA was useful in quantitating inhibin-A in biol. fluids, with little crossreactivity to free  $\alpha$ -chain or inhibin-B.

L2 ANSWER 17 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1994:161141 CAPLUS

DN 120:161141

TI Inhibition of human lung cancer cell line growth by an anti-p185HER2 antibody

AU Kern, Jeffrey A.; Torney, Lisa; Weiner, David; Gazdar, Adi; Shepard, H. Michael; \*\*\*Fendly, Brian\*\*\*

CS Dep. Med., Univ. Iowa, Iowa City, IA, 52242, USA

SO Am. J. Respir. Cell Mol. Biol. (1993), 9(4), 448-54

CODEN: AJRBEL; ISSN: 1044-1549

DT Journal

LA English

Adonis  
QP 121. A4 A48

AB P185HER2, the product of the c-erbB-2 or HER2 gene, is a membrane-bound tyrosine kinase that has structural similarity to the epidermal growth factor receptor. Functionally, interaction of HER2 with its ligand or p185HER2 antibodies affects the growth and differentiation of HER2-expressing breast cancer cell lines. As p185HER2 is also expressed in human lung cancers and human lung cancer cell lines, the authors hypothesized that these cell lines would also respond to p185HER2 antibodies. To test this hypothesis, the authors cultured human non-small cell lung cancer cell lines in the presence of a p185HER2 monoclonal antibody called 4D5. 4D5 inhibited the growth of p185HER2-expressing cell lines in a dose-dependent fashion. In addn., BEAS.2B, a p185HER2-nonexpressing bronchial epithelial cell line, was transfected with the HER2 cDNA, resulting in high-level p185HER2 expression, and growth of BEAS.HER2 was now inhibited by 4D5 exposure. Mechanistically, 4D5 appeared to have a weak agonist effect on the tyrosine kinase function of p185HER2, as exposure of p185HER2-expressing cell lines to 4D5 resulted in increased p185HER2 phosphorylation. Furthermore, inhibition of tyrosine kinase function with genistein reversed the 4D5-induced growth inhibition. Therefore, 4D5 can regulate the growth of p185HER2-expressing lung cancer cell lines through agonist effects on p185HER2.

L2 ANSWER 18 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1994:131847 CAPLUS

DN 120:131847

TI Differential responses of human tumor cell lines to anti-p185HER2 monoclonal antibodies

AU Lewis, Gail D.; Figari, Irene; \*\*\*Fendly, Brian\*\*\*; Wong, Wai Lee; Carter, Paul; Gorman, Cori; Shepard, H. Michael

CS Genentech Inc., South San Francisco, CA, 94080, USA

SO Cancer Immunol. Immunother. (1993), 37(4), 255-63

CODEN: CIIMDN; ISSN: 0340-7004

DT Journal

LA English

AB The HER2 protooncogene encodes a receptor tyrosine kinase, p185HER2.

The overexpression of p185HER2 has been assocd. with a worsened prognosis in certain human cancers. In the present work the authors have screened a variety of different tumor cell lines for p185HER2 expression using both enzyme-linked immunosorbent and fluorescence-activated cell sorting assays employing murine monoclonal antibodies directed against the extracellular domain of the receptor. Increased levels of p185HER2 were found in breast (5/9), ovarian (1/6), stomach (2/3) and colorectal (5/16) carcinomas, whereas all kidney and submaxillary adenocarcinoma cell lines tested were neg. Some monoclonal antibodies directed against the extracellular domain of p185HER2 inhibited growth in monolayer culture of breast and ovarian tumor cell lines overexpressing p185HER2, but had no effect on the growth of colon or gastric adenocarcinomas expressing increased levels of this receptor. The most potent growth-inhibitory anti-p185HER2 monoclonal antibody in monolayer culture, designated mumAb 4D5 (a murine IgG1k antibody), was also tested in soft-agar growth assays for activity against p185HER2-overexpressing tumor cell lines of each type, with similar results. In order to increase the spectrum of tumor types

RC Z61.A1 C27

potentially susceptible to monoclonal antibody-mediated anti-p185HER2 therapies, to decrease potential immunogenicity issues with the use of murine monoclonal antibodies for human therapy, and to provide the potential for antibody-mediated cytotoxic activity, a mouse/human chimeric 4D5 (chmAb 4D5) and a "humanized" 4D5 (rhu)mAb 4D5 HER2 antibody were constructed. Both engineered antibodies, in combination with human peripheral blood mononuclear cells, elicited antibody-dependent cytotoxic responses in accordance with the level of p185HER2 expression. Since this cytotoxic activity is independent of sensitivity to mumAb 4D5, the engineered monoclonal antibodies expand the potential target population for antibody-mediated therapy of human cancers characterized by the overexpression of p185HER2.

L2 ANSWER 19 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1994:189126 CAPLUS

DN 120:189126

TI Successful immunization of rhesus monkeys with the extracellular domain of p185HER2: a potential approach to human breast cancer

AU \*\*\*Fendly, Brian M.\*\*\* ; Kotts, Claire; Wong, Wai Lee T.; Figari, Irene; Harel, William; Staib, Ludger; Carver, Monique E.; Vetterlein, David; Mitchell, Malcolm S.; Shepard, H. Michael

CS Dep. Med. Anal. Chem., Genentech, Inc., South San Francisco, CA, 94808, USA

SO Vaccine Res. (1993), 2(3), 129-39

CODEN: VAREES; ISSN: 1056-7909

DT Journal

LA English

AB The HER2/neu (HER2) protooncogene is found to be amplified in a variety of human adenocarcinomas and its overexpression predicts a worsened patient prognosis. One approach to aid in the treatment of these aggressive malignancies is to direct the patient's own immune system toward those tumor cells that overexpress HER2. A potential cancer vaccine for this purpose, the extracellular domain of the HER2 gene product (HER2-ECD), has been evaluated for immunogenicity in rhesus monkeys. The extracellular domain alone was weakly immunogenic in one of five monkeys. In contrast, the HER2-ECD administered in combination with Detox adjuvant was immunogenic in four of five monkeys. The sera from two monkeys that received HER2-ECD plus Detox demonstrated growth inhibitory activities in vitro on a breast tumor cell line (SK-BR-3) that overexpressed the HER2 protooncogene. Sera from these monkeys also mediated antibody-dependent cellular cytotoxicity specific to tumor cell lines overexpressing the protooncogene. Cell-mediated immunity was also present. Lymphocytes from four of five monkeys proliferated in vitro when stimulated by HER2-ECD. Antigen-primed cells from three of five monkeys showed strong, and two somewhat lesser, cell-mediated cytotoxicity toward tumor cells overexpressing HER2. At least one parameter of immunity against HER2 was elevated in all five monkeys given both HER2-ECD and Detox. These findings indicate that the extracellular domain of the HER2 gene product fulfills two important criteria required of a cancer antigen by stimulating both the humoral and cellular compartments of the immune response.

L2 ANSWER 20 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1993:641463 CAPLUS

DN 119:241463

TI Monoclonal antibody based ELISAs for measurement of activins in biological fluids

AU Wong, Wai Lee T.; Garg, Shaily J.; Woodruff, Teresa; Bald, Laura; \*\*\*Fendly, Brian\*\*\* ; Lofgren, James A.

CS Department of Medicinal and Analytical Chemistry, and, San Francisco, CA, 94080, USA

SO J. Immunol. Methods (1993), 165(1), 1-10

CODEN: JIMMBG; ISSN: 0022-1759

DT Journal

LA English

AB Two sensitive monoclonal antibody (MAb)-based enzyme-linked immunosorbent assays (ELISAs), one for activin A (homodimer of .beta.A subunits) and one for activin B (homodimer of .beta.B subunits) in plasma have been developed. The activin A ELISA had an effective range of 0.2-50 ng/mL, whereas the activin B ELISA's range was 0.1-25 ng/mL in human serum. Both ELISAs were specific with <0.01% cross-reactivity with related hormones and follistatin (an activin-binding protein); however, the presence of recombinant human follistatin caused a decrease in measured level of activin A and B spiked human samples. The assay was linear across the std. curve range with intra- and interassay coeffs. of variation were less than 15%. The level of activins in female serum range from 0.3 to 10.4 ng/mL. In summary, the authors have developed a reliable, convenient and rapid MAb-based enzyme immunoassay for detn. of activin A and B levels in human serum which are also applicable for buffer, mouse and monkey serum matrixes. This assay will be useful for studying the regulation and role of activin A and B in health and disease.

L2 ANSWER 21 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1992:564031 CAPLUS

DN 117:164031

TI Human natriuretic peptide receptor-A guanylyl cyclase. Hormone cross-linking and antibody reactivity distinguish receptor glycoforms

AU Lowe, David G.; \*\*\*Fendly, Brian M.\*\*\*

CS Dep. Mol. Biol., Genentech, Inc., South San Francisco, CA, 94080, USA

SO J. Biol. Chem. (1992), 267(30), 21691-7

CODEN: JBCHA3; ISSN: 0021-9258

DT Journal

LA English

AB Most of the physiol. actions of atrial natriuretic peptide (ANP) may be attributed to activation of the natriuretic peptide receptor-A (NPR-A) guanylyl cyclase. It is reported here that truncation of the NPR-A cytoplasmic domain results in increased expression of cell surface ANP binding sites. The truncated receptor exhibited a hyperbolic time course for ANP binding and had a high affinity for [125I]hANP,  $K_d = 8$  pM. Cells expressing truncated NPR-A were used as an immunogen to obtain monoclonal antibodies against the native conformation of the extracellular domain. These antibodies were used to select for high levels of stable NPR-A expression in 293 cells, by fluorescence-activated cell sorting. Disuccinimidyl

suberate cross-linked [125I]ANP to 135-kDa NPR-A on intact cells. Monoclonal antibody immunopptn. of 35S-labeled proteins revealed NPR-A size heterogeneity, with 135- and 125-kDa species. A synthetic peptide antibody directed against the extracellular domain immunopptd. 125-kDa NPR-A, but recognized both sizes of receptor by Western blotting. The 125-kDa NPR-A did not bind to or cross-link ANP. NPR-A size variants were expressed on the cell surface, and heterogeneity was removed by deglycosylation with protein:N-glycosidase F. Results suggest that the degree of N-linked glycosylation of the NPR-A extra-cellular domain influences the ability to bind ANP.

L2 ANSWER 22 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1992:549050 CAPLUS

DN 117:149050

TI Biochemical properties of the 75-kDa tumor necrosis factor receptor.  
Characterization of ligand binding, internalization, and receptor phosphorylation

AU Pennica, Diane; Lam, Van T.; Mize, Nancy K.; Weber, Richard F.;  
Lewis, Martyn; \*\*\*Fendly, Brian M.\*\*\* ; Lipari, Michael T.;  
Goeddel, David V.

CS Dep. Mol. Biol., Genentech, Inc., South San Francisco, CA, 94080,  
USA

SO J. Biol. Chem. (1992), 267(29), 21172-8

CODEN: JBCHA3; ISSN: 0021-9258

DT Journal

LA English

AB An expression plasmid encoding the human 75-kDa tumor necrosis factor (TNF) type 2 receptor (TNF-R2) was constructed and used to generate a stable human cell line (293/TNF-R2) overexpressing TNF-R2. Ligand binding anal. revealed high affinity binding ( $K_d = 0.2$  nM) with approx. 94,000 sites/cell for 125I-TNF-.alpha. and approx. 5-fold lower affinity for TNF-.beta. ( $K_d = 1.1$  nM) with 264,000 sites/cell. Crosslinking of 125I-TNF-.alpha. and 125I-TNF-.beta. to 293/TNF-R2 cells yielded predominant complexes with apparent mol. wts. of 211,000 for TNF-.alpha. and 205,000 and 244,000 for TNF-.beta., suggesting these complexes contain 2 or 3 TNF-R2 mols. Immunopptn. of TNF-R2 from 32P-labeled 293/TNF-R2 cells demonstrated that the receptor is phosphorylated. The majority (97%) of 32Pi incorporation was found in serine residues with a very low level of incorporation (3%) in threonine residues. TNF-.alpha. treatment of 293/TNF-R2 cells did not affect the degree or pattern of phosphorylation. Cell surface-bound 125I-TNF-.alpha. was slowly internalized by the 293/TNF-R2 cell line with a  $t_{1/2} = 25$  min. Shedding of the extracellular domain of TNF-R2 was induced by 4.beta.-phorbol 12-myristate 13-acetate but not by TNF-.alpha. or TNF-.beta..

L2 ANSWER 23 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1992:192352 CAPLUS

DN 116:192352

TI Identification of cysteine-rich domains of the type 1 tumor necrosis factor receptor involved in ligand binding

AU Marsters, Scot A.; Frutkin, Andrew D.; Simpson, Nancy J.;  
\*\*\*Fendly, Brian M.\*\*\* ; Ashkenazi, Avi

CS Dep. Immunobiol., Genentech, Inc., South San Francisco, CA, 94080, USA

SO J. Biol. Chem. (1992), 267(9), 5747-50

CODEN: JBCHA3; ISSN: 0021-9258

DT Journal

LA English

AB The extracellular portion of the type 1 (p55) and type 2 (p75) tumor necrosis factor (TNF) receptors contains a repetitive amino acid sequence pattern of four cysteine-rich domains (CRDs). This pattern is found also in several other cell surface proteins, including the p75 nerve growth factor receptor and the CD40, 4-1BB, OX40, Fas, and CD27 antigens. To investigate whether CRDs play a role in TNF binding, the authors have constructed sol. variants of the extracellular portion of human type 1 TNF receptor (sTNFR1), in which CRD1 (N-terminal) or CRD4 (C-terminal) was deleted by mutagenesis. These variants or a wild type sTNFR1 were linked in their C terminus to the hinge and Fc portion of IgG1 heavy chain to create sTNFR1-IgG chimeras (immunoadhesins). Deletion of either CRD1 or -4 did not cause any major perturbations in the structure of the sTNFR1 variants, as evidenced by their efficient expression and secretion from transfected cells, and by their binding to conformation-dependent monoclonal antibodies that recognize diverse epitopes on sTNFR1. The wild type sTNFR1 immunoadhesin exhibited high affinity binding to TNF.alpha. ( $K_d = 65 \text{ pM}$ ) and TNF.beta. ( $K_d = 640 \text{ pM}$ ). Deletion of CRD4 resulted in about a 10-fold redn. in affinity for TNF.alpha. ( $K_d = 660 \text{ pM}$ ) and for TNF.beta. ( $K_d = 5.7 \text{ nM}$ ). In contrast, deletion of CRD1 resulted in a complete loss of binding to TNF.alpha. and to TNF.beta.. These results indicate that CRD4 is important but not necessary for TNF binding, while CRD1 is required. In addn., the results suggest some overlap between the TNFR1 binding sites for TNF.alpha. and TNF.beta., despite low amino acid sequence homol. between these cytokines.

L2 ANSWER 24 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1992:403400 CAPLUS

DN 117:3400

TI Radiolabeled antibody targeting of the HER-2/neu oncoprotein

AU De Santes, Kenneth; Slamon, Dennis; Anderson, Susan K.; Shepard, Michael; \*\*\*Fendly, Brian\*\*\*; Maneval, Daniel; Press, Oliver

CS Dep. Pediatr., Univ. Washington, Seattle, WA, 98195, USA

SO Cancer Res. (1992), 52(7), 1916-23

CODEN: CNREA8; ISSN: 0008-5472

DT Journal

LA English

AB The HER-2/neu oncogene encodes a Mr 185,000 transmembrane phosphoglycoprotein which is overexpressed in 25-35% of breast and ovarian neoplasms and portends a poor prognosis. The feasibility was studied of targeting this oncoprotein, designated p185, with radioiodinated murine monoclonal antibodies (muMABs) 4D5 and 7C2, which recognize distinct epitopes on its extracellular domain. The rates of internalization and catabolism of these antibodies were analyzed by cellular RIA and electron microscopy. After binding to NIH3T3 HER-2/neu cells, which show high surface expression of p185, the muMABs were endocytosed via coated pits, routed to lysosomes, and degraded. Approx. 44% of 125I-4D5 and 39% of 125I-7C2 were

catabolized by tumor cells after 24 h. The biodistribution of radiolabeled 4D5 and 7C2 were evaluated in beige/nude mice bearing s.c. NIH3T3 HER-2/neu grafts. A high specificity of localization was seen with tumor-to-organ ratios of activity generally ranging from 5:1 to 30:1. However, the percent injected dose of radioactivity per g of tumor declined sharply from 25% at 24 h to 5% at 120 h postinjection. Treating the animals with 400-700 .mu.Ci 131I-4D5 caused a marked inhibition of tumor growth, although no mice were cured. Unlabeled 4D5 had no effect on tumor progression in this model, but administering 400-700 .mu.Ci of 131I-DA4-4, an isotype-matched irrelevant muMAB, resulted in an intermediate degree of growth retardation. Anal. of kinetic blood data and whole-body time-activity curves indicated that the irrelevant conjugate remained in the body 2-3-fold longer than 131I-4D5. Radioiodinated anti-HER-2/neu muMABs are attractive agents for radioimmunodiagnosis and radioimmunotherapy of aggressive HER-2/neu-pos. breast and ovarian carcinomas, but effective strategies for retarding intratumoral catabolism may be necessary to optimize their clinical utility.

L2 ANSWER 25 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1992:166553 CAPLUS

DN 116:166553

TI Passive immunoneutralization with a monoclonal antibody reveals a role for endogenous activin-B in mediating FSH hypersecretion during estrus and following ovariectomy of hypophysectomized, pituitary-grafted rats

AU DePaolo, Louis V.; Bald, Laura N.; \*\*\*Fendly, Brian M.\*\*\*

CS Dep. Mol. Endocrinol., Whittier Inst. Diabetes and Endocrinol., La Jolla, CA, 92037, USA

SO Endocrinology (Baltimore) (1992), 130(3), 1741-3

CODEN: ENDOAO; ISSN: 0013-7227

DT Journal

LA English

AB Ovariectomy (OVX)-induced FSH hypersecretion can be elicited in hypophysectomized rats bearing renal pituitary allografts isolated from direct hypothalamic intervention. The possible role of the FSH-stimulating protein, activin-B, in eliciting this response was investigated using passive immunoneutralization with a monoclonal antibody (MAb) generated against activin-B. Other hypophysectomized/pituitary-grafted (H/G) rats serving as controls received an equiv. amt. of a MAb incapable of neutralizing the biological actions of activin-B. Administration of increasing doses of the MAb prior to OVX dose-dependently suppressed serum FSH levels 12 h after OVX. Less consistent effects were observed 24 h after OVX, even though an additional injection of the MAb was given 12 h after OVX in one study. Since it has been postulated that the periovulatory increase in FSH secretion on estrus (which is important for recruitment of follicles) is a hypothalamic-independent phenomenon, a separate experiment was performed to ascertain whether a local regulatory mechanism involving activin-B is operative on estrus. As in the preceding study using H/G rats, administration of the activin-B MAb on the evening of proestrus attenuated serum FSH rises early on estrus. These results are consonant with the evolving concept that an important mechanism exists within the anterior pituitary proper for



regulation of FSH secretion that involves the autocrine actions of activin-B.

L2 ANSWER 26 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1992:57008 CAPLUS

DN 116:57008

TI Characterization of a recombinant extracellular domain of the type 1 tumor necrosis factor receptor: evidence for tumor necrosis factor .alpha. induced receptor aggregation

AU Pennica, Diane; Kohr, William J.; \*\*\*\*Fendly, Brian M.\*\*\* ; Shire, Steven J.; Raab, Helga E.; Borchardt, Paul E.; Lewis, Martyn; Goeddel, David V.

CS Dep. Mol. Biol., Genentech, Inc., South San Francisco, CA, 94080, USA

SO Biochemistry (1992), 31(4), 1134-41

CODEN: BICHAW; ISSN: 0006-2960

DT Journal

LA English

AB An expression plasmid encoding the extracellular portion of the human tumor necrosis factor (TNF) type 1 receptor (TNF-R1) was constructed and used to generate a stable cell line secreting sol. TNF-R1 (sTNF-R1). The sTNF-R1 was purified, and its biochem. properties and its interaction with human TNF-.alpha. were examd. SDS-PGE resolved the purified sTNF-R1 into 3 bands of approx. mol. wt. (Mr) 24,200, 28,200, and 32,800. Sedimentation equil. anal. gave a 25,000 for sTNF-R1 whereas the value obtained by gel filtration chromatog. was approx. 55,000-60,000. Scatchard anal. of [125I]TNF-.alpha. binding to sTNF-R1 revealed high affinity binding ( $K_d = 93$  pM), comparable to that obsd. for the intact receptor on whole cells. Competitive binding expts. showed that sTNF-R1 has a 50-60-fold higher affinity for TNF-.alpha. than for TNF-.beta., in contrast to the equal affinities of TNF-.alpha.- and TNF-.beta. for the full length TNF-R1 transiently expressed in mammalian cells. The sTNF-R1 was found to block the cytotoxicity of TNF-.alpha. and TNF-.beta. on a murine L-M cell assay. The sizes of the sTNF-R1 TNF-.alpha. complex detd. by gel filtration chromatog. and sedimentation equil. were approx. 141 and 115 kDa, resp. The stoichiometry of the complex was examd. by Scatchard anal., size-exclusion chromatog., HPLC sepn., amino acid compn., sequence anal, and sedimentation equil. The data from these studies suggest that at least 2 mols. of sTNF-R1 can bind to a single TNF-.alpha. trimer. It is proposed that the initiation of signaling by TNF-R1 involves TNF-.alpha.-induced receptor oligomerization.

L2 ANSWER 27 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1993:447107 CAPLUS

DN 119:47107

TI High resolution functional analysis of antibody-antigen interactions

AU Jin, Lei; \*\*\*\*Fendly, Brian M.\*\*\* ; Wells, James A.

CS Dep. Protein Eng., Genentech, Inc., South San Francisco, CA, 94080, USA

SO J. Mol. Biol. (1992), 226(3), 851-65

CODEN: JMOBAK; ISSN: 0022-2836

DT Journal

LA English

AB A comprehensive mutational anal. was used to analyze the side-chains on human growth hormone (hGH) important for binding 21 different anti-hGH mouse monoclonal antibodies (MAbs) whose equiv. concns. for 50% binding (EC50) ranged from .apprx.107 to 3 .times. 1010 M-1. A combination of homolog- and alanine-scanning mutagenesis coupled with a robot-aided ELISA were used to create high resoln. functional epitopes for each MAb. Every functional epitope mapped to at least 2 polypeptide segments of hGH that were close together in the folded protein to form a patch. Although these patches sometimes overlapped, each was different indicating no 2 MAbs bound identically to hGH. The MAbs bound to determinants in loops and helices that were generally most accessible to a 9 .ANG. radius probe. Only a few side-chains dominated each functional epitope and these tended to be Arg > Pro > Glu .apprx. Asp .apprx. Phe .apprx. Ile (Ala, Cys, and Trp were not tested). Thus, most of the accessible surface of hGH is potentially antigenic in the mouse and functional epitopes are dominated by fewer side-chains than may be in the contact epitope.

L2 ANSWER 28 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1992:82048 CAPLUS

DN 116:82048

TI Uncleaved human immunodeficiency virus (HIV) envelope polypeptides, their preparation, their use in vaccination against HIV, and monoclonal antibodies to the polypeptides

IN Berman, Phillip W.; \*\*\*Fendly, Brian M.\*\*\* ; Gregory, Timothy J.; Wurm, Florian M.

PA Genentech, Inc., USA

SO PCT Int. Appl., 71 pp.

CODEN: PIXXD2

PI WO 9115238 A1 19911017

DS W: AU, CA, JP

RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE

AI WO 91-US2250 19910401

PRAI US 90-504785 19900403

DT Patent

LA English

AB Uncleaved HIV envelope polypeptides gp120 and gp160, and fragments thereof, are provided; these polypeptides are not proteolytically cleaved at an internal cleavage site. Also disclosed are their prepn. and use in vaccines against HIV, as well as monoclonal antibodies (MAbs) against them. Thus, using an optimized immunization protocol, chimpanzees were immunized with, e.g., rgp120 (recombinant gp120 fragment of HIV-1 envelope glycoprotein fused to a short amino-terminal sequence of herpes simplex virus glycoprotein D). Combined results suggested that immunization with rgp120 elicited a protective immune response which significantly delayed or completely prevented infection of the animals by HIV-1. The MAbs of the invention define .apprx.11 epitopes on gp160. Six of the MAbs inhibited binding of gp120 to the CD4 receptor. Of these 6, 3 were able to neutralize HIV virions, as indicated by redn. of reverse transcriptase activity in vitro. Three other MAbs also neutralized infectious virions in the in vitro assay. Prepn. of uncleaved gp120 via recombinant cell culture is described.

L2 ANSWER 29 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1991:406706 CAPLUS

DN 115:6706

TI Long-term inhibition of tumor growth by tumor necrosis factor in the absence of cachexia or T-cell immunity

AU Teng, Michael N.; Park, Ben H.; Koeppen, Hartmut K. W.; Tracey, Kevin J.; \*\*\*Fendly, Brian M.\*\*\* ; Schreiber, Hans

CS Dep. Pathol., Univ. Chicago, Chicago, IL, 60637, USA

SO Proc. Natl. Acad. Sci. U. S. A. (1991), 88(9), 3535-9

CODEN: PNASA6; ISSN: 0027-8424

DT Journal

LA English

AB The relationship between detrimental (cachectic) and beneficial (antitumor) effects of tumor necrosis factor (TNF) was studied in mice bearing murine tumors transfected to secrete human TNF. In vitro, the TNF-producing transfectants were resistant to the secreted TNF and grew at rates similar to those of untransfected cells or transfected cells that did not secrete TNF. However, tumors formed by the TNF-secreting cells in vivo remained much smaller than the nonsecreting (transfected and nontransfected) tumors. This inhibition of tumor growth required only relatively low serum levels of TNF, persisted for many weeks, and was independent of T cells since it occurred in nude mice. Growth of the TNF-secreting tumors increased dramatically after treatment with anti-human TNF antibody, indicating that extracellular TNF secreted by the tumor cells was necessary for the tumor inhibition. Severe wt. loss characteristic of cachexia only occurred in animals with very high serum TNF levels (250 pg/mL) and could be prevented or reversed by anti-TNF antibody treatment. Thus, there exists a therapeutic window in which persistent exposure to human TNF can lead to prolonged inhibition of tumor growth in the absence of T-cell immunity or severe wt. loss and without development of resistant tumor variants.

L2 ANSWER 30 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1991:157365 CAPLUS

DN 114:157365

TI Evidence for an autocrine role of activin B within rat anterior pituitary cultures

AU Corrigan, Anne Z.; Bilezikjian, Louise M.; Carroll, Rona S.; Bald, Laura N.; Schmelzer, Charles H.; \*\*\*Fendly, Brian M.\*\*\* ; Mason, Anthony J.; Chin, William W.; Schwall, Ralph H.; Vale, Wylie

CS Clayton Found. Lab. Pept. Biol., Salk Inst., La Jolla, CA, USA

SO Endocrinology (Baltimore) (1991), 128(3), 1682-4

CODEN: ENDOAO; ISSN: 0013-7227

DT Journal

LA English

AB Activins, dimers of inhibin .beta. subunits, are potent simulators of FSH secretion in vivo and in vitro and of FSH.beta. mRNA expression in rat anterior pituitary cultures. In this study, the possibility that locally secreted activin B (.beta.B.beta.B) may function as an autocrine modulator of basal FSH secretion and expression was studied in rat anterior pituitary cells in culture. The incubation of cultured cells with a mouse monoclonal antibody specific for the activin B homodimer (MAb-activin B) significantly

attenuated the basal secretion of FSH in a concn. - and time-dependent manner, without influencing LH secretion. Moreover, MAb-activin B selectively inhibited FSH.beta. mRNA accumulation without affecting either LH.beta. or .alpha. subunit mRNAs. The MAb-activin B completely blocked the stimulation of FSH secretion by exogenous activin B, but not by activin A, confirming its specificity. As previously shown, inhibin A and follistatin significantly suppressed basal FSH secretion in these cultures. This inhibitory effect, albeit of lower magnitude, was still evident even in the presence of the MAb-activin B which by itself suppressed basal FSH secretion. These data suggest that the secretion of activin B by the gonadotrophs of the anterior pituitary may serve as an autocrine signal in the selective modulation of FSH expression and secretion. Furthermore, the inhibitory actions of inhibins and follistatins on gonadotrophs may, in part, be explained by their ability to interfere with the actions of endogenous activin B.

L2 ANSWER 31 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1991:550702 CAPLUS

DN 115:150702

TI Generation of antibodies and assays for transforming growth factor .beta.

AU Lucas, Catherine; \*\*\*Fendly, Brian M.\*\*\* ; Mukku, Venkat R.; Wong, Wai Lee; Palladino, Michael A.

CS Dep. Med. Anal. Chem., Gentech, Inc., South San Francisco, CA, 94080, USA

SO Methods Enzymol. (1991), 198(Pept. Growth Factors, Pt. C), 303-16  
CODEN: MENZAU; ISSN: 0076-6879

DT Journal

LA English

AB This paper describes the prodn. of monoclonal antibodies specific for transforming growth factor (TGF)-.beta.1 and the radiolabeling of this protein. These reagents together with human TGF-.beta.1 from recombinant sources were used for the development of a double-antibody enzyme immunoassay and a RIA specific for TGF-.beta.1. Also described are a radioreceptor assay and a bioactivity assay for TGF-.beta..

L2 ANSWER 32 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1991:653452 CAPLUS

DN 115:253452

TI Monoclonal antibody therapy of human cancer: taking the HER2 protooncogene to the clinic

AU Shepard, H. Michael; Lewis, Gail D.; Sarup, Jay C.; \*\*\*Fendly,\*\*\*  
\*\*\* Brian M.\*\*\* ; Maneval, Daniel; Mordenti, Joyce; Figari, Irene;  
Kotts, Claire E.; Palladino, Michael A., Jr.; et al.

CS Dep. Dev. Biol., Genentech, Inc., South San Francisco, CA, 94080, USA

SO J. Clin. Immunol. (1991), 11(3), 117-27  
CODEN: JCIMDO; ISSN: 0271-9142

DT Journal; General Review

LA English

AB A review, with 35 refs., on: the HER2 protooncogene and human cancer; derivation of muMAb 4D5; in vivo preclin. efficacy; and mechanism of action.

*Adams  
RC581. J68*

L2 ANSWER 33 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1992:610447 CAPLUS

DN 117:210447

TI TGF-.beta.: a possible autocrine immune regulator

AU Lucas, Catherine; Wallick, Susan; \*\*\*Fendly, Brian M.\*\*\* ;  
Figari, Irene; Palladino, Michael A.

CS Dep. Med. Anal. Chem., Genentech Inc., South San Francisco, CA,  
94080, USA

SO Ciba Found. Symp. (1991), 157(Clin. Appl. TGF-.beta. [beta]), 98-114  
CODEN: CIBSB4; ISSN: 0300-5208

DT Journal

LA English

AB TGF-.beta. is a potent regulator of immune functions both in vitro and in vivo. The majority of studies have examd. changes in immune functions after the addn. of TGF-.beta. that had been previously activated by acid treatment. Peripheral blood mononuclear cells (PBMC) and tumor cells can each produce latent TGF-.beta.. The role of endogenously produced latent TGF-.beta. as an autocrine or paracrine regulator of immune fractions has not been extensively studied. Monoclonal antibody (mAb) 4A11 was used to detect and neutralize the activity of endogenous TGF-.beta.1 produced during lymphocyte activation. PBMC, after stimulation with interleukin 2 or phytohemagglutinin-P/12-O-tetradecanoylphorbol 13-acetate, secrete significant quantities of latent TGF-.beta.1. Addn. of neutralizing mAbs specific for TGF-.beta.1 enhances the proliferative response of the PBMC. CHO cell lines engineered to produce latent TGF-.beta.1 were poor stimulators of cytotoxic T lymphocyte generation in vivo and significantly suppress natural killer cell activity in nu/nu mice. Thus mechanisms exist in vitro and in vivo to convert latent TGF-.beta. into an active form which can then regulate immune functions in an autocrine/paracrine manner. The possible role of latent TGF-.beta. produced by tumor cells in immune surveillance is discussed.

L2 ANSWER 34 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1990:589551 CAPLUS

DN 113:189551

TI Mapping the CD4 binding site for human immunodeficiency virus by alanine-scanning mutagenesis

AU Ashkenazi, Avi; Presta, Leonard G.; Marsters, Scot A.; Camerato, Thomas R.; Rosenthal, Kim A.; \*\*\*Fendly, Brian M.\*\*\* ; Capon, Daniel J.

CS Dep. Mol. Biol., Genentech, South San Francisco, CA, 94080, USA

SO Proc. Natl. Acad. Sci. U. S. A. (1990), 87(18), 7150-4

CODEN: PNASA6; ISSN: 0027-8424

DT Journal

LA English

AB Infection of mononuclear cells by human immunodeficiency virus (HIV) begins with binding of the viral envelope glycoprotein, gp120, to its receptor, CD4. CD4 contains four extracellular Ig-like domains, the first of which (V1) is sufficient for HIV binding. V1 contains three sequences homologous to the antigen-complementarity-detg. regions (CDR1 to -3) of Ig variable domains. While all three Ig CDRs are involved in antigen binding, only amino acids within and

flanking the CDR2-like region of CD4 have been shown previously to be involved in gp120 binding. To investigate whether other regions in V1 take part in gp120 binding, alanine was substituted for each of 64 amino acids, including all of the hydrophilic residues in this domain. Mutations at four locations outside the CDR2-like sequence (amino acids 29, 59-64, 77-81, and 85) markedly affected gp120 binding, but not the overall structure of V1 as probed with eight conformationally sensitive monoclonal antibodies. Thus, the gp120-binding site of CD4 is not limited to the CDR2-like sequence and consists of several discontinuous segments. Several amino acids were identified that are crit. for the conformation of V1; the importance of these residues suggests some differences in the folding of this domain compared to Ig variable domains. Three amino acid substitutions were found that increase the affinity for gp120 (1.7- to 2-fold individually and 4.2-fold when combined), suggesting that it may be possible to improve the HIV-blocking ability of CD4-based mols. by increasing their gp120 binding affinity.

L2 ANSWER 35 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1990:176642 CAPLUS

DN 112:176642

TI Characterization of murine monoclonal antibodies reactive to either the human epidermal growth factor receptor or HER2/neu gene product

AU \*\*\*Fendly, Brian M.\*\*\* ; Winget, Marcy; Hudziak, Robert M.;

Lipari, Michael T.; Napier, Mary Anna; Ullrich, Axel

CS Dep. Med. Anal. Chem., Genentech, Inc., South San Francisco, CA, 94080, USA


SO Cancer Res. (1990), 50(5), 1550-8

CODEN: CNREA8; ISSN: 0008-5472

DT Journal

LA English

AB High levels of expression of either the epidermal growth factor receptor or the receptor-like HER2/neu gene product p185HER2 have been obsd. in a variety of human malignancies. Because of the assocn. of this high level expression with certain human tumors, the authors have generated a panel of monoclonal antibodies specific for either the epidermal growth factor receptor or p185HER2 to study their structure, function, and antigenic domains in the normal and neoplastic states. The epidermoid carcinoma line A431 was used to generate five monoclonal antibodies which immunoppt. the epidermal growth factor receptor. These monoclonal antibodies bind to the extracellular domain of the epidermal growth factor receptor and demonstrate variable effects on epidermal growth factor binding. A stably transfected NIH 3T3 cell line expressing the HER2/neu gene was used to produce and characterized 10 monoclonal antibodies which immunoppt. p185HER2. These monoclonal antibodies bind to the extracellular domain of p185HER2 and do not cross-react with the epidermal growth factor receptor.



L2 ANSWER 36 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1990:589422 CAPLUS

DN 113:189422

TI The autocrine production of transforming growth factor-.beta.1 during lymphocyte activation. A study with a monoclonal antibody-based ELISA

AU Lucas, Catherine; Bald, Laura N.; \*\*\*Fendly, Brian M.\*\*\* ;  
Mora-Worms, Marina; Figari, Irene S.; Patzer, Eric J.; Palladino,  
Michael A.

CS Dep. Med. Anal. Chem., Genentech. Inc., South San Francisco, CA,  
94080, USA

SO J. Immunol. (1990), 145(5), 1415-22

CODEN: JOIMA3; ISSN: 0022-1767

DT Journal

LA English

AB The prodn. and characterization of three mAb to transforming growth factor-.beta. (TGF-.beta.) and the use of two of them for the development of a TGF-.beta.1-specific ELISA and for the study of the regulation of immune function in vitro are described. All three mAb bound recombinant human TGF-.beta.1 (rHuTGF-.beta.1) with high affinity and recognized the dimer form of this mol. in immunoblots. MAb 2G7 immunopptd. rHuTGF-.beta.1, TGF-.beta.2, and rHuTGF-.beta.3 and neutralized the growth inhibitory activity of all three mols. in vitro on mink lung epithelial-like cells, Mv1Lu, indicating a shared neutralization epitope. MAb 4A11 neutralized and immunopptd. only rHuTGF-.beta.1, and mAb 12H5 immunopptd. rHuTGF-.beta.1 but had no effect on the bioactivity of either rHuTGF-.beta.1, TGF-.beta.2, or rHuTGF-.beta.3. These results suggest that a second neutralization epitope may be unique to TGF-.beta.1. The ELISA was developed with mAb 4A11 and 12H5, with a range of 0.63 to 40 ng/mL, i.e., a sensitivity of 0.63 ng/mL or 63 pg/sample. The assay is accurate, precise, and specific for the active but not the inactive or latent TGF-.beta.1 complex. Supernatants obtained from serum-free cultures of human PBMC from multiple donors contained significant quantities of TGF-.beta.1 (3 to 15 ng/mL), which was detected in the ELISA only after pH 2 treatment to convert latent TGF-.beta. to the active form. Treatment of the PBMC with either recombinant human IL-2 (rHuIL-2) or PHA-P/PMA enhanced the prodn. of latent TGF-.beta.. MAb 4A11 and 2G7, but not mAb 12H5, enhanced both the proliferative response of PBMC to rHuIL-2/rHuTNF-.alpha. and PHA-P and the development of the rHuIL-2/rHuTNF-.alpha. treated PBMC into LAK cells with cytotoxic activity against COLO target cells. These findings suggest that although PBMC secrete latent TGF-.beta.1, mechanisms that convert the latent TGF-.beta. complex into an active form exist in vitro and that the endogenously produced TGF-.beta. can regulate immune functions in an autocrine fashion.

L2 ANSWER 37 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1990:509472 CAPLUS

DN 113:109472

TI Increase in cyclic AMP levels by relaxin in newborn rhesus monkey uterus cell culture

AU Kramer, Susan Mukavitz; Gibson, Ursula E. M.; \*\*\*Fendly, Brian\*\*\*  
\*\*\* M.\*\*\* ; Mohler, Marjorie A.; Drolet, Daniel W.; Johnston, Paul D.

CS Dep. Assay Dev., Genentech, Inc., South San Francisco, CA, 94080,  
USA

SO In Vitro Cell. Dev. Biol. (1990), 26(6), 647-56

CODEN: ICDBEO; ISSN: 0883-8364

DT Journal

LA English

AB A novel relaxin sensitive cell line of apparent smooth muscle origin

was established from a newborn rhesus monkey uterus (NRMU). NRMU cells response to relaxin, in the presence of 1 .mu.M forskolin, by producing intracellular cAMP. The increase in cAMP levels is dose, time, and cell d. dependent, reaching peak levels at 10 min when cells are seeded at 1 .times. 105 cells/well. Specificity was demonstrated by neutralization of the relaxin activity with anti-relaxin monoclonal and polyclonal antibodies, degrdn. of cAMP in the presence of phosphodiesterase, and confirmation of the absence of cGMP. Three synthetic analogs of human relaxin generated a dose-related cAMP response as did synthetic native human relaxin. Natural relaxin purified from human corpora lutea tissue also generated a response similar to synthetic human relaxin. Porcine and rat relaxins also increased levels of cAMP. Insulin, but not IGF I or IGF II, was capable of increasing cAMP levels in NRMU cells, however, 200 ng/mL were required to achieve cAMP levels comparable to 6.25 ng/mL relaxin. Combinations of relaxin with insulin, IGF I, or IGF II did not increase cAMP levels above levels obtained with relaxin alone. The effect on NRMU cells of other hormones, growth factors and drugs potentially present in cell culture system or serum samples was evaluated. In combination with relaxin, oxytocin decreased the cAMP prodn. below the levels induced by relaxin alone, whereas progesterone and PGE2 resulted in additive increases in cAMP. Apparently, the NRMU cell line is an appropriate target tissue for studying relaxin-mediated biol. responses in vitro as well as functioning as the primary component of a relaxin in vitro bioassay.

L2 ANSWER 38 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1990:530201 CAPLUS

DN 113:130201

TI Mammalian cell transient expression of tissue factor for the production of antigen

AU Paborsky, Lisa R.; \*\*\*Fendly, Brian M.\*\*\* ; Fisher, Karen L.; Lawn, Richard M.; Marks, Billie J.; McCray, Glynis; Tate, Keri M.; Vehar, Gordon A.; Gorman, Cornelia M.

CS Dep. Cardiovasc. Res., Genentech, Inc., So. San Francisco, CA, 94080, USA

SO Protein Eng. (1990), 3(6), 547-53

CODEN: PRENE9; ISSN: 0269-2139

DT Journal

LA English

AB A mammalian cell expression system was used to rapidly produce microgram quantities of a membrane protein used as an immunogen. A fusion protein expression vector was constructed which contained the signal sequence and 27 amino acids of the Herpes simplex virus glycoprotein D (gD), followed by a factor VIII (fVIII) thrombin cleavage site and the mature tissue factor (TF) sequence. This fusion protein was transiently expressed and then purified using an antibody to gD. The purified fusion protein, gD<sup>TF</sup>, was incubated with thrombin to remove the gD-fVIII moiety and the resulting rTF served as antigen for the generation of TF-specific antibodies. The antibodies produced were then used for a comparison of the turnover rates of the constitutively and transiently produced fusion protein. In addn., sensitivity to glycosidases indicated that the transiently and constitutively produced recombinant proteins do not contain



identical carbohydrate structures.

L2 ANSWER 39 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1991:40817 CAPLUS

DN 114:40817

TI The extracellular domain of HER2/neu is a potential immunogen for active specific immunotherapy of breast cancer

AU \*\*\*Fendly, Brian M.\*\*\* ; Kotts, Claire; Vetterlein, David; Lewis, Gail D.; Winget, Marcy; Carver, Monique E.; Watson, Susan R.; Sarup, Jay; Saks, Sam; et al.

CS Genentech, Inc., South San Francisco, CA, 94080, USA

SO J. Biol. Response Modif. (1990), 9(5), 449-55

CODEN: JBRMDS; ISSN: 0732-6580

DT Journal

LA English

AB The proto-oncogene HER2/neu encodes a protein tyrosine kinase (p185HER2) that is homologous to the human epidermal growth factor receptor. Amplification and/or overexpression of HER2/neu occurs in multiple human malignancies and appears to be integrally involved in progression of some breast and ovarian cancers. Because of this fact, HER2/neu is an intriguing target for specific immunotherapy, in which the immune system is targeted at specific antigens expressed by tumor cells. A transfected cell line that secretes the extracellular domain of p185HER2 as a source of HER2-derived immunogen was employed in a guinea pig model. The immunized animals developed a cellular immune response, as monitored by delayed-type hypersensitivity, and antisera derived from immunized animals specifically inhibited the in vitro growth of human breast tumor cells overexpressing p185HER2. These data provide support for an immunotherapeutic approach to cancers characterized by overexpression of the HER2/neu proto-oncogene.

L2 ANSWER 40 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1990:175161 CAPLUS

DN 112:175161

TI A monoclonal-antibody-based enzyme-linked immunosorbent assay of lipoprotein(a)

AU Lee, Wai; Wong, T.; Eaton, Dan L.; Berloui, Azita; \*\*\*Fendly,\*\*\*  
\*\*\* Brian\*\*\* ; Hass, Philip E.

CS Dep. Immunol. Res. Assay Technol., Genentech, Inc., San Francisco, CA, 94080, USA

SO Clin. Chem. (Winston-Salem, N. C.) (1990), 36(2), 192-7

CODEN: CLCHAU; ISSN: 0009-9147

DT Journal

LA English

AB The recent awareness of a striking correlation between atherosclerosis and concns. of lipoprotein (a) [Lp(a)] in plasma prompted the development of an accurate quant. assay for plasma Lp(a), a monoclonal-antibody-based ELISA for Lp(a) that is shown to be sensitive, precise, and highly specific. The response to several isoforms of Lp(a) is linear, and as many as 80 samples can be quantified on one plate. This easily performed assay is suitable for use in the clin. lab. and for screening large populations.

L2 ANSWER 41 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1989:451120 CAPLUS

DN 111:51120

TI Epidermal growth factor and transforming growth factor .alpha. bind differently to the epidermal growth factor receptor

AU Winkler, Marjorie E.; O'Connor, Lynn; Winget, Marcy; \*\*\*Fendly,\*\*\*  
\*\*\* Brian\*\*\*

CS Dep. Med. Biomol. Chem., Genentech Inc., South San Francisco, CA, 94080, USA

SO Biochemistry (1989), 28(15), 6373-8

CODEN: BICHAW; ISSN: 0006-2960

DT Journal

LA English

AB Epidermal growth factor (EGF) and transforming growth factor-.alpha. (TGF.alpha.) compete with each other for binding to the EGF receptor. These 2 growth factors have similar actions, but there are distinguishable differences in their biol. activities. It has never been clear how this one receptor can mediate different responses. A monoclonal antibody to the EGF receptor (13A9) has been identified which has only small effects on the binding of EGF to the EGF receptor purified from human A431 cells, but which has very large effects on the binding of TGF.alpha. to the EGF receptors; 5 .mu.g/mL of the antibody has been shown to totally block 0.87 .mu.M TGF.alpha. from binding to purified EGF receptor and to lower both the high- and low-affinity binding consts. of TGF.alpha. binding to EGF receptor on A431 cells by about 10-fold. The 13A9 antibody causes a 2.5-fold stimulation of the tyrosine kinase activity of partially purified EGF receptor, compared with a 4.0-fold stimulation of the tyrosine kinase activity by EGF under the same conditions. The data suggest that either the antibody stabilizes a conformation of the EGF receptor which is not favorable for TGF.alpha. binding, or it blocks a part of the surface of the receptor which is necessary for TGF.alpha. binding but not EGF binding.

L2 ANSWER 42 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1989:551710 CAPLUS

DN 111:151710

TI Liposome-associated tumor necrosis factor retains bioactivity in the presence of neutralizing anti-tumor necrosis factor antibodies

AU Debs, Robert J.; Duzgunes, Nejat; Brunette, Elisa N.; \*\*\*Fendly,\*\*\*  
\*\*\* Brian\*\*\* ; Patton, John; Philip, Ramila

CS Cancer Res. Inst., Univ. California, San Francisco, CA, 94143-0128, USA

SO J. Immunol. (1989), 143(4), 1192-7

CODEN: JOIMA3; ISSN: 0022-1767

DT Journal

LA English

AB Cell-assocd. tumor necrosis factor-.alpha. (TNF-.alpha.), either bound to its receptor on monocyte membranes or expressed as an integral membrane protein, can exert potent tumor cytolytic activity. The interaction was assessed of TNF with the lipid bilayer membrane system, liposomes, and the effects of membrane assocn. on TNF bioactivity. High levels of TNF can be encapsulated within liposomes. At neutral pH, TNF binds to the surface of preformed liposomes (liposome-assocd. TNF), but does not partition

into the lipid bilayer. TNF appears to bind to neg. charged phospholipid head groups of the outer membrane leaflet. Free TNF, liposome-assocd. TNF, and liposome-encapsulated TNF display comparable abilities to activate human peripheral blood monocytes and to lyse tumor cells. However, liposome-encapsulated TNF, as well as TNF bound to the outer surface of preformed liposomes, retains bioactivity in the presence of anti-TNF antibodies that neutralize free TNF. The interaction of liposomal TNF with cell surface TNF receptors thus appears to be preserved in the presence of neutralizing antibodies.

L2 ANSWER 43 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1989:190916 CAPLUS

DN 110:190916

TI p185HER2 Monoclonal antibody has antiproliferative effects in vitro and sensitizes human breast tumor cells to tumor necrosis factor

AU Hudziak, Robert M.; Lewis, Gail D.; Winget, Marcy; \*\*\*Fendly,\*\*\*  
\*\*\* Brian M.\*\*\* ; Shepard, H. Michael; Ullrich, Axel

CS Dep. Dev. Biol., Genentech, Inc., South San Francisco, CA, 94080,  
USA

SO Mol. Cell. Biol. (1989), 9(3), 1165-72

CODEN: MCEBD4; ISSN: 0270-7306

DT Journal

LA English

AB The HER2/c-erbB-2 gene encodes the epidermal growth factor receptor-like human homolog of the rat neu oncogene. Amplification of this gene in primary breast carcinomas has been shown to correlate with poor clin. prognosis for certain cancer patients. It is shown here that a monoclonal antibody directed against the extracellular domain of p185HER2 specifically inhibits the growth of breast tumor-derived cell lines overexpressing the HER2/c-erbB-2 gene product and prevents HER2/c-erbB-2-transformed NIH 3T3 cells from forming colonies in soft agar. Resistance to the cytotoxic effect of tumor necrosis factor .alpha., which has been shown to be a consequence of HER2/c-erbB-2 overexpression, is decreased in the presence of this antibody.

L2 ANSWER 44 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1989:73770 CAPLUS

DN 110:73770

TI Monoclonal antibodies against C5a and de-Arg74-C5a, their production and use

IN Larrick, James W.; \*\*\*Fendly, Brian M.\*\*\* ; Deinhart, Tracey E.

PA Cetus Corp., USA

SO Eur. Pat. Appl., 14 pp.

CODEN: EPXXDW

PI EP 245993 A2 19871119

DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE

AI EP 87-303762 19870428

PRAI US 86-856780 19860428

US 86-947839 19861230

DT Patent

LA English

AB Monoclonal antibodies which bind to human complement C5a are prepd. for treatment of conditions assocd. with injurious intravascular

complement activation and for detection of C5a or de-Arg74-C5a (I) (a C5a metabolite) in body fluids. Mouse monoclonal antibodies to human C5a were prepd. by the hybridoma method. Injection of anti-C5a antibody 260-91H-2G-10D i.p. into rabbits produced a much smaller disappearance of polymorphs from the blood than injection of a control antibody (not against C5a), indicating that the anti-C5a antibody blocks the effect of C5a in vivo.

L2 ANSWER 45 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1988:508822 CAPLUS

DN 109:108822

TI Monoclonal antibodies to *Pseudomonas aeruginosa* exoenzyme S, their preparation and use

IN Markowitz, Avi B.; \*\*\*Fendly, Brian\*\*\* ; Iglewski, Barbara; Larrick, James

PA Cetus Corp., USA; Oregon Health Sciences University

SO Eur. Pat. Appl., 9 pp.

CODEN: EPXXDW

PI EP 243174 A2 19871028

DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE

AI EP 87-303543 19870422

PRAI US 86-855005 19860422

DT Patent

LA English

AB Monoclonal antibodies to *P. aeruginosa* exoenzyme S (I) are prepd. from hybrid cell lines. Those antibodies that can neutralize the adverse biol. effects of I may be used to treat infections caused by *P. aeruginosa*. The antibodies are also used to detect I. Murine hybridomas secreting monoclonal antibodies specific to I were prepd. by immunizing Balb/c mice with purified I in phosphate-buffered saline contg. 0.1% SDS and Freund's adjuvant and fusing the spleen cells with 653 or SP2/0 myeloma cells. The hybrid cells were cloned and screened with I ELISA. Monoclonal antibodies 4F7, 1F6, 10F10, and 15D4 were selected and analyzed in enzyme neutralization tests.

L2 ANSWER 46 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1987:552405 CAPLUS

DN 107:152405

TI Characterization of murine monoclonal antibodies that recognize neutralizing epitopes on human C5a

AU Larrick, James W.; Wang, Jeff; \*\*\*Fendly, Brian M.\*\*\* ; Chenoweth, Dennis E.; Kunkel, Steven L.; Deinhart, Tracy

CS Cetus Immune Res. Labs, Palo Alto, CA, 94303, USA

SO Infect. Immun. (1987), 55(8), 1867-72

CODEN: INFIBR; ISSN: 0019-9567

DT Journal

LA English

AB A panel of 10 murine monoclonal antibodies (MAbs) was generated that recognize human complement C5a. These MAbs were characterized for their ability to immunoppt. <sup>125</sup>I-labeled C5a, bind C5a in solid-phase EIA, and block <sup>125</sup>I-labeled C5a binding to polymorphonuclear leukocytes. Four of these MAbs had affinity consts. for C5a in the 1 .times. 10<sup>9</sup> to 3 .times. 10<sup>9</sup> M<sup>-1</sup> range. These MAbs blocked C5a-induced neutrophil polarization and chemiluminescence. They blocked the ability of passively

administered C5a to cause neutropenia in rabbits.

L2 ANSWER 47 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1987:117855 CAPLUS

DN 106:117855

TI Recombinant tumor necrosis factor causes activation of human granulocytes

AU Larrick, James W.; Graham, Delores; Toy, Karen; Lin, Leo S.; Senyk, George; \*\*\*\*Fendly, Brian M.\*\*\*

CS Med. Cent., Stanford Univ., Palo Alto, CA, 94303, USA

SO Blood (1987), 69(2), 640-4

CODEN: BLOOAW; ISSN: 0006-4971

DT Journal

LA English

AB The authors tested the hypothesis that tumor necrosis factor (TNF), by binding to and activating granulocytes, may contribute to the pathogenesis of gram-neg. sepsis and the adult respiratory distress syndrome (ARDS). Buffy coat granulocytes incubated with as little as 0.5 ng/mL of recombinant TNF (rTNF) showed a dose-related increase in nitroblue tetrazolium dye redn., in granulocyte polarization, in superoxide anion release, and in visually apparent aggregation. Purified lipopolysaccharide (1 .mu.g/mL) caused polymorphonuclear (PMN) aggregation and activation that was neutralized by polymyxin B. The release of superoxide was augmented by preincubation of the PMNs with .gamma.-interferon. The effect of TNF was neutralized by TNF-specific murine monoclonal antibodies but not by polymyxin B. Scatchard anal. of 125I-labeled rTNF binding to granulocytes revealed about 1200 receptors per cell with a dissocn. const. of 4.9 .times. 10<sup>-10</sup> mol/L. Apparently, the release of TNF by mononuclear phagocytes contributes to granulocyte activation and aggregation during inflammation.

L2 ANSWER 48 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1987:573878 CAPLUS

DN 107:173878

TI Murine monoclonal antibodies defining neutralizing epitopes on tumor necrosis factor

AU \*\*\*\*Fendly, Brian M.\*\*\* ; Toy, Karen J.; Creasey, Abba A.; Vitt, Charles R.; Larrick, James W.; Yamamoto, Ralph; Lin, Leo S.

CS Cetus Immune Res. Lab., Palo Alto, CA, 94303, USA

SO Hybridoma (1987), 6(4), 359-70

CODEN: HYBRDY; ISSN: 0272-457X

DT Journal

LA English

AB A panel of 4 monoclonal antibodies (MAbs) was generated against recombinant human tumor necrosis factor-.alpha. (rTNF). These MAbs immunoppt. 125I-labeled rTNF, block binding of 125I-labeled rTNF to L929 mouse fibroblasts, and neutralize in vitro cytotoxicity of rTNF and native TNF in the L929 cytotoxicity assay. They define distinct epitopes closely assocd. with the receptor binding site of rTNF. Two MAbs recognizing distinct epitopes were used to develop a sandwich enzyme immunometric assay to measure rTNF levels in human serum and other fluids.

L2 ANSWER 49 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1986:570273 CAPLUS

DN 105:170273

TI Species-specific monoclonal antibody to a 43,000-molecular-weight membrane protein of *Mycoplasma pneumoniae*

AU Madsen, Randall D.; Saeed, Fawzia A.; Gray, Oanh; \*\*\*Fendly, Brian\*\*\*

\*\*\* M.\*\*\* ; Coates, Stephen R.

CS Cetus Corp., Emeryville, CA, 94608, USA

SO J. Clin. Microbiol. (1986), 24(4), 680-3

CODEN: JCMIDW; ISSN: 0095-1137

DT Journal

LA English

AB A murine IgG1 monoclonal antibody was produced that binds to a protease-sensitive, periodate-insensitive epitope on a 43,000-mol.-wt. *M. pneumoniae* membrane polypeptide. The 43,000-mol.-wt. polypeptide appeared to be a major antigenic component of *M. pneumoniae*, as detd. by immunoblot anal. This monoclonal antibody reacted with 33 different clin. isolates of *M. pneumoniae*, but not with normal-flora *Mycoplasma* species or 18 other microorganisms potentially inhabiting the normal or diseased human respiratory tract. This apparent species-specific monoclonal antibody may have application for the detection of *M. pneumoniae* antigen in clin. specimens.

L2 ANSWER 50 OF 50 CAPLUS COPYRIGHT 1998 ACS

AN 1983:213806 CAPLUS

DN 98:213806

TI Protein A binding assay for the identification of HLA antigens on peripheral blood lymphocytes by monoclonal antibodies: application to HLA B27

AU Yang, Y. H. Joy; Grumet, F. Carl; \*\*\*Fendly, Brian\*\*\* ; Engleman, Edgar; Shively, John E.

CS Div. Immunol., City of Hope Res. Inst., Duarte, CA, 91010, USA

SO Hybridoma (1982), 1(3), 243-55

CODEN: HYBRDY; ISSN: 0272-457X

DT Journal

LA English

AB Splenocytes from mice immunized with purified, papain-solubilized HLA B27 antigen and/or human lymphocytes bearing the B27 specificity were fused with myeloma cell lines NS1 or Sp2. The monoclonal antibody screening strategy employed a protein A binding assay in which various target cells were used. First, the hybrid cell supernatants were screened against B lymphocyte cell lines of known HLA specificities and the Daudi cell line, which does not express HLA-A, B, or C antigens. Second, a panel of peripheral blood lymphocytes (PBLs) were used as target cells. It was necessary to refine the protein A binding assay by preabsorbing the radiolabeled protein A with PBLs and by precoating the test wells with ovalbumin. Clones selected by these criteria were further tested by indirect immunopptn. and by inhibition of binding or microcytotoxicity to target cell lines with purified HLA antigens or .beta.2-microglobulin (.beta.2m). Forty-four clones were selected which showed varying degrees of specificity for allo- and nonallo-specific HLA determinants and 1 clone was selected which was specific for .beta.2m. Clone 27M1, which was previously shown to be specific for HLA-B27 as judged by conventional microcytotoxicity testing, was

compared with other clones using the above parameters for evaluation. Antibody from clone 27M1 showed preferential binding to B27 pos. cell lines and PBLs, lesser binding to B7 pos. target cells, and no binding to B40 pos. target cells. Purified B27 antigen from 2 sources, including the B27 target cell line, was able to inhibit the binding of antibodies from 27M1 to target cells. The extension of the protein A binding assay to PBLs has made it possible to more accurately quantitate the binding or inhibition of binding of antibodies to panels of PBLs.

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 E11 2 PHILLIPS GARRY D/AU  
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L4 1 "PHILLIPS GAIL DIANNE"/AU

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L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 1998 ACS

AN 1998:268615 CAPLUS

DN 128:307524

TI Antibodies to the neu receptor capable of inducing apoptosis and their therapeutic uses

IN Fendly, Brian M.; \*\*\*Phillips, Gail Dianne\*\*\* ; Scheuermann, Richard H.; Uhr, Jonathan W.

PA Genentech, Inc., USA; Board of Regents, the University of Texas System

SO PCT Int. Appl., 77 pp.

CODEN: PIXXD2

PI WO 9817797 A1 19980430

DS W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG

AI WO 97-US18385 19971009

PRAI US 96-731794 19961018

DT Patent

LA English

AB Anti-ErbB2 antibodies that bind to an epitope in Domain 1 of the receptor (the neu receptor) and induce cell death via apoptosis are described. These antibodies have a no. of uses, e.g. in the treatment of ovarian cancer and in detection of overexpression of

the erbB2 gene.

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E5 1 SCHEUERMANN RICHARD HARVEY/AU  
E6 1 SCHEUERMANN RONALD F/AU  
E7 10 SCHEUERMANN S/AU  
E8 1 SCHEUERMANN S B/AU  
E9 63 SCHEUERMANN S E/AU  
E10 1 SCHEUERMANN STEFAN/AU  
E11 1 SCHEUERMANN STEFAN E/AU  
E12 1 SCHEUERMANN SUSANNE/AU

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L5 26 ("SCHEUERMANN RICHARD"/AU OR "SCHEUERMANN RICHARD H"/AU  
OR "SCHEUERMANN RICHARD HARVEY"/AU)

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YOU HAVE REQUESTED DATA FROM 26 ANSWERS - CONTINUE? Y/(N):y

L6 ANSWER 1 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1998:268615 CAPLUS

DN 128:307524

TI Antibodies to the neu receptor capable of inducing apoptosis and  
their therapeutic uses

IN Fendly, Brian M.; Phillips, Gail Dianne; \*\*\*Scheuermann, Richard\*\*\*  
\*\*\* H.\*\*\* ; Uhr, Jonathan W.

PA Genentech, Inc., USA; Board of Regents, the University of Texas  
System

SO PCT Int. Appl., 77 pp.

CODEN: PIXXD2

PI WO 9817797 A1 19980430

DS W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,  
DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR,  
KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,  
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG,  
UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB,  
GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG

AI WO 97-US18385 19971009

PRAI US 96-731794 19961018

DT Patent

LA English

AB Anti-ErbB2 antibodies that bind to an epitope in Domain 1 of the  
receptor (the neu receptor) and induce cell death via apoptosis are  
described. These antibodies have a no. of uses, e.g. in the  
treatment of ovarian cancer and in detection of overexpression of  
the erbB2 gene.

L6 ANSWER 2 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1998:122480 CAPLUS



DN 128:242747

TI Cancer dormancy: role of cyclin-dependent kinase inhibitors in induction of cell cycle arrest mediated via membrane IgM

AU Marches, Radu; \*\*\*Scheuermann, Richard H.\*\*\* ; Uhr, Jonathan W.

CS Cancer Immunobiology Center and Department of Microbiology, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, 75235-8576, USA

SO Cancer Res. (1998), 58(4), 691-697

CODEN: CNREA8; ISSN: 0008-5472

PB American Association for Cancer Research

DT Journal

LA English

AB Anti-idiotypic (anti-Id) antibody can induce tumor dormancy in a murine B lymphoma, BCL1, by its ability to induce cell cycle arrest and apoptosis (neg. signaling). In human B lymphoma, there is accumulating evidence that the antitumor effect of anti-Id or several other B cell-reactive antibodies relates to their ability to act as agonists rather than conventional effector antibodies. In this study, we sought to elucidate the role of cyclins, cyclin-dependent kinases (CDKs), and their inhibitors in anti-IgM-induced cell cycle arrest to better understand the mechanisms underlying cancer dormancy. To accomplish this, we have performed in vitro studies with a human lymphoma cell line (Daudi) because its response to anti-Id (or anti-IgM) is similar to that of a BCL1 cell line, more reagents are available, and the results would be particularly pertinent to therapy of human B cell lymphomas. Our results show that crosslinking of membrane IgM on Daudi cells induces an arrest late in G1 and prevents pRb from becoming phosphorylated. The G1 arrest is correlated with an induction of the CDK inhibitor p21 and reduced CDK2 activity, although the level of CDK2 protein was not changed. Copptn. of CDK2 with p21 in anti-IgM-treated cells and the unchanged level of cyclin E suggest that p21 is responsible for the redn. of CDK2 activity and therefore blockade of the cell cycle. The induction of p21 was not accompanied by changes in p53 levels. As a result of the G1 block, cyclin A levels sharply declined by 24 h after anti-IgM treatment. There was no evidence for involvement of CDK4 or CDK6 in the blockade. These results provide evidence that membrane IgM crosslinking on Daudi cells induces expression of p21 and a subsequent inhibition of the cyclin E-CDK2 kinase complex resulting in a block to pRb phosphorylation and cell cycle arrest late in G1.

L6 ANSWER 3 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1998:292050 CAPLUS

DN 129:51662

TI Analytical performance of a quantitative CMV DNA detection method

AU Reagan, Kevin J.; Cabradilla, Cy; Shuman, Barry; Stollar, Neil; Laudemann, Joerg; Bai, Xin; Hosler, Gregory; \*\*\*Scheuermann,\*\*\*  
\*\*\* Richard H.\*\*\*

CS BioSource International, Inc., Camarillo, CA, USA

SO Monogr. Virol. (1998), 21(CMV-Related Immunopathology), 252-261

CODEN: MONVAK; ISSN: 0077-0965

PB S. Karger AG

DT Journal

LA English

AB This report describes the anal. performance of a competitive polymerase chain reaction (PCR) procedure for detecting CMV DNA. CMV DNA was isolated from whole blood, plasma, buffy coat or other samples. The internal calibration std. (ICS) is constructed to contain PCR primer binding sites identical to the CMV DNA and a unique capture binding site to allow the resulting ICS amplicon to be distinguished from the CMV amplicon. CMV primers, targeting a conserved sequence of gB (gpUL55), are provided in the Viral Quant format for inclusion in the PCR mix. During amplification, the biotin-labeled primer is incorporated into both ICS and CMV amplicons. Following PCR, the amplicons are denatured and hybridized to either ICS or CMV sequence-specific capture oligonucleotides which are prebound to microtiter wells. The bound amplicons are detected and quantified by addn. of an enzyme-streptavidin conjugate followed by substrate. The ICS, amplified at an efficiency identical to the CMV DNA, serves as a std. for CMV DNA quantitation. The anal. sensitivity, linear range, and efficiency of this detection system are discussed, as well as results in healthy controls and CMV-infected patients.

L6 ANSWER 4 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1998:186965 CAPLUS

TI Benefits and dangers of genetic tests

AU \*\*\*Scheuermann, Richard H.\*\*\* ; Picker, Louis J.

CS Dep. Pathol., Univ. Texas, Dallas, TX, 75235-9072, USA

SO Nature (London) (1998), 392(6671), 14

CODEN: NATUAS; ISSN: 0028-0836

PB Macmillan Magazines

DT Journal; Letter

LA English

AB Unavailable

L6 ANSWER 5 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1997:735837 CAPLUS

DN 128:10314

TI Anti-CD19 and anti-CD22 monoclonal antibodies and immunotoxins and therapeutic uses thereof

IN Uhr, Jonathan W.; Vitetta, Ellen S.; \*\*\*Scheuermann, Richard H.\*\*\*

PA Board of Regents, the University of Texas, USA

SO U.S., 34 pp. Cont.-in-part of U.S. Ser. No. 899,781, abandoned.

CODEN: USXXAM

PI US 5686072 A 19971111

AI US 94-202042 19940222

PRAI US 92-899781 19920617

DT Patent

LA English

AB The anti-tumor activity of a mixt. of anti-CD22 and anti-CD19 immunotoxins is shown to be significantly enhanced in SCID/Daudi mice with disseminated human Daudi lymphoma. Unexpectedly identical enhancement was obsd. employing a combination of the anti-CD22 immunotoxin with unconjugated anti-CD19 antibodies. Thus combinations of an anti-CD22 immunotoxin and an anti-CD19 immunotoxin or antibody act synergistically and provide advantageous compns. and methods for immunotherapeutic treatment of various diseases including cancer and autoimmune disorders. Also disclosed

is data indicating that certain anti-CD19 antibodies alone inhibit proliferation of CD19-pos. cells by inducing cell cycle arrest.

L6 ANSWER 6 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1997:394674 CAPLUS

DN 127:107881

TI Tumor dormancy and cell signaling. V. Regrowth of the BCL1 tumor after dormancy is established

AU Vitetta, Ellen S.; Tucker, Thomas F.; Racila, Emilian; Huang, Yi-Wu; Marches, Radu; Lane, Nancy; \*\*\*Scheuermann, Richard H.\*\*\* ; Street, Nancy E.; Watanabe, Takeshi; Uhr, Jonathan W.

CS Cancer Immunobiology Center, Dep. Microbiol. Pathol., Univ. Texas Southwestern Medical Center Dallas, Dallas, TX, 75235, USA

SO Blood (1997), 89(12), 4425-4436

CODEN: BLOOAW; ISSN: 0006-4971

PB Saunders

DT Journal

LA English

AB The majority of BALB/c mice immunized with the BCL1 lymphoma-derived idiotype (Id+) IgM and subsequently challenged with BCL1 tumor cells develop a state of tumor dormancy. The vast majority of dormant lymphoma cells are in cell cycle arrest, but there are also residual replicating cells. In the present studies, the authors attempted to define features of both the dormant lymphoma cells and the host that lead to escape from dormancy. Escape from dormancy occurs at a steady rate over a 2-yr period, suggesting that it is a stochastic process. The authors found that, in the majority of mice, escape was due to the emergence of genetic variants that were no longer susceptible to the anti-Id-mediated induction of dormancy. Ten percent of these variants were Id-; the remainder were Id+ but could grow in the presence of anti-Id antibodies, suggesting that there were mutations in mols. involved in one or more mIg-mediated neg.-signaling pathways. In two of five such escapees, alterations in either Syk, HS1, and/or Lyn were obsd. In a small percentage of mice, a low titer of circulating anti-Id antibody before tumor challenge correlated with a subsequent, more rapid loss of dormancy.

L6 ANSWER 7 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1997:675232 CAPLUS

DN 127:355707

TI Quantitative polymerase chain reaction for human herpesvirus diagnosis and measurement of Epstein-Barr virus burden in posttransplant lymphoproliferative disorder

AU Bai, Xin; Hosler, Gregory; Rogers, Beverly Barton; Dawson, D. Brian; \*\*\*Scheuermann, Richard H.\*\*\*

CS Department of Pathology and Laboratory of Molecular Pathology, University of Texas Southwestern Medical Center, Dallas, TX, 75235-9072, USA

SO Clin. Chem. (Washington, D. C.) (1997), 43(10), 1843-1849

CODEN: CLCHAU; ISSN: 0009-9147

PB American Association for Clinical Chemistry

DT Journal

LA English

AB Human herpesviruses can cause acute diseases such as chicken pox or mononucleosis, but also may reactivate during immunosuppression and

result in severe or life-threatening illnesses such as shingles or lymphoproliferative disorders. The authors report the development and validation of a quant. PCR method to measure viral burden for all eight human herpesviruses (HSV1, HSV2, VZV, EBV, CMV, HHV6, HHV7, and KSHV) in patients' samples. The method uses an internal std. that is coamplified with the viral target, allowing quantification of viral genomes in abs. terms (e.g., viral targets/mL of blood) and ruling out false-neg. results. The authors demonstrate that transplant patients with lymphoproliferative disorder carry an EBV viral burden 3 logs higher than nontransplant patients. EBV titers in transplant patients without a lymphoproliferative disorder are between these values. This quant. PCR method may aid in differentiating clin. significant vs latent viral burden in immunosuppressed patients.

L6 ANSWER 8 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1997:297504 CAPLUS

DN 127:15970

TI Cancer dormancy: opportunities for new therapeutic approaches

AU Uhr, Jonathan W.; \*\*\*Scheuermann, Richard H.\*\*\* ; Street, Nancy E.; Vitetta, Ellen S.

CS Cancer Immunobiol. Cent. and Dep. Microbiol., Univ. Texas Southwest Med. Cent., Dallas, TX, 75235, USA

SO Nat. Med. (N. Y.) (1997), 3(5), 505-509

CODEN: NAMEFI; ISSN: 1078-8956

PB Nature Publishing Co.

DT Journal; General Review

LA English

AB A review, with 59 refs. Topics discussed include: host responses involved in dormancy, the immune system, escape from dormancy, future diagnostic and therapeutic approaches, inducing dormancy in epithelial tumors, and combination immunotherapy.

L6 ANSWER 9 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1996:252907 CAPLUS

DN 124:287019

TI A role for c-myc in the regulation of thymocyte differentiation and possibly positive selection

AU Broussard-Diehl, Christine; Bauer, Steven R.; \*\*\*Scheuermann,\*\*\*  
\*\*\* Richard H.\*\*\*

CS Grad. Program Immunol., UT Southwestern Med. Cent., Dallas, TX, 75235, USA

SO J. Immunol. (1996), 156(9), 3141-50

CODEN: JOIMA3; ISSN: 0022-1767

DT Journal

LA English

AB The purpose of thymocyte differentiation is to establish the T cell repertoire and eliminate nonfunctional and autoreactive T cells. In an anal. of potential regulators of this process, we have found that c-myc expression is down-regulated dramatically during early thymocyte differentiation and subsequently up-regulated along with TCR/CD3 in CD4+8+ cells. Transgenic E.beta.-myc mice that constitutively express c-myc in thymocytes have a larger proportion of thymocytes with high TCR/CD3 and low heat-stable antigen-1 expression than controls, and an increase in the no. of transitional

cells with a CD4+CD8low phenotype. Mature E.beta.-myc T cells respond less vigorously than controls to activation through their TCR/CD3 complex, as measured by proliferation and induction of the activation marker CD69. These results are consistent with a hypothesis in which activation of immature T cells through TCR/CD3 induces c-myc up-regulation and drives thymocytes through the initial stage of pos. selection.

L6 ANSWER 10 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1996:152900 CAPLUS

DN 124:229870

TI Tumor dormancy and cell signaling: anti-.mu.-induced apoptosis in human B-lymphoma cells is not caused by an APO-1-APO-1 ligand interaction

AU Racila, Emilian; Hsueh, Robert; Marches, Radu; Tucker, Thomas F.; Krammer, Peter H.; \*\*\*Scheuermann, Richard H.\*\*\* ; Uhr, Jonathan W.

CS Cancer Immunobiol. Cent., Univ. Texas Southwest. Med. Cent., Dallas, TX, 75235, USA

SO Proc. Natl. Acad. Sci. U. S. A. (1996), 93(5), 2165-8

CODEN: PNASA6; ISSN: 0027-8424

DT Journal

LA English

AB Signal transduction initiated by crosslinking of antigen-specific receptors on T- and B-lymphoma cells induces apoptosis. In T-lymphoma cells, such crosslinking results in upregulation of the APO-1 ligand, which then interacts with induced or constitutively expressed APO-1, thereby triggering apoptosis. Here the authors show that crosslinking the membrane Ig on human lymphoma cells (Daudi) (that constitutively express APO-1) does not induce synthesis of APO-1 ligand. Further, a noncytotoxic fragment of anti-APO-1 antibody that blocks T-cell-receptor-mediated apoptosis in T-lymphoma cells does not block anti-.mu.-induced apoptosis. Hence, in B-lymphoma cells, apoptosis induced by signaling via membrane IgM is not mediated by the APO-1 ligand.

L6 ANSWER 11 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1997:252654 CAPLUS

DN 126:262848

TI Role of antibody signaling in inducing tumor dormancy

AU Uhr, Jonathan W.; Marches, Radu; Racila, Emil; Tucker, Thomas F.; Hsueh, Robert; Street, Nancy E.; Vitetta, Ellen S.; \*\*\*Scheuermann, Richard H.\*\*\*

CS Department of Microbiology and Cancer Immunobiology Center, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, 75235-8576, USA

SO Adv. Exp. Med. Biol. (1996), 406(Mechanisms of Lymphocyte Activation and Immune Regulation VI), 69-74

CODEN: AEMBAP; ISSN: 0065-2598

PB Plenum

DT Journal; General Review

LA English

AB A review with 32 refs. The authors discuss the effect of hypercrosslinking receptors on signaling in B lymphoma cells, the role of APO-1 ligand in IgM-mediated apoptosis, and regrowth of

dormant tumor (escape).

L6 ANSWER 12 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1995:880342 CAPLUS

DN 123:308124

TI Mutually exclusive interaction of a novel matrix attachment region binding protein and the NF- $\kappa$ B enhancer repressor. Implications for regulation of immunoglobulin heavy chain expression

AU Zong, Rui-Ting; \*\*\*Scheuermann, Richard H.\*\*\*

CS Lab. Mol. Pathol., Univ. Texas Southwestern Med. Cent., Dallas, TX, 75235-9072, USA

SO J. Biol. Chem. (1995), 270(41), 24010-18

CODEN: JBCHA3; ISSN: 0021-9258

DT Journal

LA English

AB The Ig heavy chain (IgH) intronic enhancer stimulates transcription from functional promoters in B lymphocytes but not other cell types. The observation that binding sites for the nuclear factor- $\kappa$ B regulator (NF- $\kappa$ B) enhancer repressor overlap nuclear matrix attachment regions (MARs) in this enhancer has led to the hypothesis that the cell type specificity of the enhancer might be controlled by regulating nuclear matrix attachment (Scheuermann, R. H., and Chen, U. (1989) Genes & Dev. 3, 1255-1266). To understand the role of MARs in IgH enhancer regulation, we have identified a novel MAR-binding protein, MAR-BP1, from sol. nuclear matrix preps. based on its ability to bind to the MARs assocd. with the IgH enhancer. Purified MAR-BP1 migrates as a 33-kDa protein, and it can be found in nuclear matrix preps. from a no. of different types of lymphoid cell lines. Although specific binding sites have been difficult to localize by chem. or enzymic footprinting procedures, NF- $\kappa$ B binding sites are crit. for efficient MAR-BP1 binding. Indeed, binding of the IgH enhancer to either intact nuclear matrix preps. or to MAR-BP1 is mutually exclusive to NF- $\kappa$ B binding. These results are consistent with a model for cell-type specific regulation in which binding of the NF- $\kappa$ B repressor to the IgH enhancer prevents nuclear matrix attachment in inappropriate cells by interfering with MAR-BP1/enhancer interaction.

L6 ANSWER 13 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1996:18835 CAPLUS

DN 124:143085

TI The immunoglobulin heavy-chain matrix-associating regions are bound by Bright: a B cell-specific trans-activator that describes a new DNA-binding protein family

AU Herrscher, Richard F.; Kaplan, Mark H.; Lelsz, David L.; Das, Chhaya; \*\*\*Scheuermann, Richard\*\*\* ; Tucker, Philip W.

CS Departments of Microbiology Pathology Immunology Graduate Program, University of Texas Southwestern Medical Center, Dallas, TX, 75235-9048, USA

SO Genes Dev. (1995), 9(24), 3067-82

CODEN: GEDEEP; ISSN: 0890-9369

DT Journal

LA English

AB B lymphocyte-restricted transcription of Ig heavy-chain (IgH) genes is specified by elements within the variable region (VH) promoter

and the intronic enhancer (E.mu.). The gene encoding a protein that binds a VH promoter proximal site necessary for induced .mu.-heavy-chain transcription has been cloned. This B-cell specific protein, termed Bright (B cell regulator of IgH transcription), is found in both sol. and matrix insol. nuclear fractions. Bright binds the minor groove of a restricted ATC sequence that is sufficient for nuclear matrix assocn. This sequence motif is present in previously described matrix-assocg. regions (MARs) proximal to the promoter and flanking E.mu.. Bright can activate E.mu.-driven transcription by binding these sites, but only when they occur in their natural context and in cell lines permissive for E.mu. activity. To bind DNA, Bright requires a novel tetramerization domain and a previously undescribed domain that shares identity with several proteins, including SWI1, a component of the SWI/SNF complex.

L6 ANSWER 14 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1995:826106 CAPLUS

DN 123:225292

TI Connections between signal transduction components and cellular responses initiated by antigen receptor on B lymphocytes

AU \*\*\*Scheuermann, Richard H.\*\*\* ; Uhr, Jonathan W.

CS Dep. of Pathology and Lab. of Mol. Pathology, Univ. of Texas Southwestern Medical Center, Dallas, TX, 75235, USA

SO J. Exp. Med. (1995), 182(4), 903-6

CODEN: JEMEAV; ISSN: 0022-1007

DT Journal; General Review

LA English

AB A review and discussion with 29 refs. on BCR receptor-mediated signaling pathways in induction of cell cycle arrest and apoptosis in B-cells. Calcium fluxes, tyrosine kinases, and phospholipase C-gamma. are important components in this system.

L6 ANSWER 15 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1994:296568 CAPLUS

DN 120:296568

TI Lyn tyrosine kinase signals cell cycle arrest but not apoptosis in B-lineage lymphoma cells

AU \*\*\*Scheuermann, Richard H.\*\*\* ; Racila, Emilian; Tucker, Thomas; Yefenof, Eitan; Street, Nancy E.; Viteita, Ellen S.; Picker, Louis J.; Uhr, Jonathan W.

CS Southwest. Med. Cent., Univ. Texas, Dallas, TX, 75235, USA

SO Proc. Natl. Acad. Sci. U. S. A. (1994), 91(9), 4048-52

CODEN: PNASA6; ISSN: 0027-8424

DT Journal

LA English

AB Signal transduction initiated by binding of antibodies to cell surface mols. can have an important impact on the growth of tumor cells. The malignant behavior of the murine lymphoma BCL1 can be suppressed and the neoplastic cells can be induced to enter a dormant state by in vivo ligation of membrane Ig. Anti-CD19 antibodies can prolong the survival of SCID mice challenged with the human Burkitt lymphoma cell line, Daudi. Here, the authors show that crosslinking of membrane Ig on both murine BCL1 and human Daudi cells initiates a cascade of signals leading to the induction of

both apoptosis and cell cycle arrest in vitro. Using antisense oligonucleotides, the authors demonstrate that the Ig-assocd. Lyn tyrosine kinase is required for anti-Ig-mediated cell cycle arrest but it not required for the signal leading to apoptosis. These results define a branch point in the cytosolic signaling pathways mediating cell cycle arrest and apoptosis. In Daudi cells, Lyn is also crit. for cell cycle arrest induced by anti-CD19 signaling. Thus, the Lyn tyrosine kinase may be an important mediator of cell cycle arrest in neoplastic B lymphocytes and, perhaps, other cell types.

L6 ANSWER 16 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1993:188975 CAPLUS

DN 118:188975

TI Cancer dormancy: Isolation and characterization of dormant lymphoma cells

AU Yefenof, Eitan; Picker, Louis J.; \*\*\*Scheuermann, Richard H.\*\*\* ; Tucker, Thomas F.; Vitetta, Ellen S.; Uhr, Jonathan W.

CS Hadassah Med. Cent., Hebrew Univ., Jerusalem, Israel

SO Proc. Natl. Acad. Sci. U. S. A. (1993), 90(5), 1829-33

CODEN: PNASA6; ISSN: 0027-8424

DT Journal

LA English

AB Tumor dormancy is a term used to describe a prolonged quiescent state in which tumor cells are present, but tumor progression is not clin. apparent. Although clin. examples of tumor dormancy abound, little is known regarding the mechanisms underlying this state. The authors utilized an antibody-induced dormancy model of an aggressive murine B-cell lymphoma (BCL1) and show that the induction of the dormant state is accompanied by changes in tumor cell morphol. and cell cycle status. These data indicate the feasibility of altering the malignant phenotype of transformed cells by specific signals originating at the cell surface, and suggest new opportunities for therapeutic intervention in cancer.

L6 ANSWER 17 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1994:51864 CAPLUS

DN 120:51864

TI Induction of B cell tumor dormancy by anti-idiotypic antibodies

AU Yefenof, Eitan; Picker, Louis J.; \*\*\*Scheuermann, Richard H.\*\*\* ; Vitetta, Ellen S.; Street, Nancy E.; Tucker, Thomas F.; Uhr, Jonathan

CS Hebrew Univ., Jerusalem, 91010, Israel

SO Curr. Opin. Immunol. (1993), 5(5), 740-4

CODEN: COPIEL; ISSN: 0952-7915

DT Journal; General Review

LA English

AB A review with 37 refs. Long-term dormancy of murine B-cell lymphomas can be exptl. induced by immunizing the host with the idiotypic expressed on the tumor. Interaction of the cells with anti-idiotypic antibodies is sufficient to induce and maintain the dormant state. The growth of lymphoma cells interacting with anti-idiotypic antibodies is arrested and they undergo dramatic changes in their morphol., cell-cycle status and oncogene expression. Regrowth of a tumor after long-term dormancy results



from the emergence of a tumor cell variant that no longer responds to the antibodies with growth inhibition. These data demonstrate the feasibility of reversing a malignant phenotype of cells by specific growth arrest signals and suggest new approaches for therapeutic intervention in cancer.

L6 ANSWER 18 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1993:552921 CAPLUS

DN 119:152921

TI Polymerase chain reaction-based mRNA quantification using an internal standard: Analysis of oncogene expression

AU \*\*\*Scheuermann, Richard H.\*\*\* ; Bauer, Steven R.

CS Southwest. Med. Cent., Univ. Texas, Dallas, TX, 75235, USA

SO Methods Enzymol. (1993), 218(Recombinant DNA, Pt. I), 446-73

CODEN: MENZAU; ISSN: 0076-6879

DT Journal

LA English

AB The authors describe a method for the quantification of mRNA levels for a set of specific protooncogenes using PCR and a synthetic RNA as an internal std. There are several advantages to the use of this procedure for mRNA quantification. First, this method provides results in terms of mols. per cell or mols. per .mu.g. Quantification in abs. nos. allows easy comparison of results from different expts. or different research groups. Second, combining PCR cycle titrn. data with the described math. anal. allows one to detect problems relating to differential amplification efficiencies of the std. and endogenous templates. Without the assessment of PCR reaction efficiencies many potential measurement errors could go undetected. Finally, PCR gives the procedure exquisite sensitivity. This kind of sensitivity is crucial for the quantification of message levels in rare cell types, or when the source of material is limited. Although the system was developed for the quantification of a set of mouse and human oncogenes, it is clear that the technique can be applied to any problem in which the measurement of mRNA levels is required.

L6 ANSWER 19 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1992:35401 CAPLUS

DN 116:35401

TI The tetrameric structure of NF-.mu.NR provides a mechanism for cooperative binding to the immunoglobulin heavy chain .mu. enhancer

AU \*\*\*Scheuermann, Richard H.\*\*\*

CS Basel Inst. Immunol., Basel, CH-4005, Switz.

SO J. Biol. Chem. (1992), 267(1), 624-34

CODEN: JBCHA3; ISSN: 0021-9258

DT Journal

LA English

AB The structure and DNA-binding characteristics of the IgH enhancer-binding regulatory protein NF-.mu.NR was analyzed. There are at least 5000 mols. of NF-.mu.NR protein/nucleus of non-B cells, based on the yield of active protein following purifn. Purified NF-.mu.NR exists as a tetramer of 40-kDa subunits, even in the absence of its DNA-binding substrate. The protein complex binds to 4 binding sites flanking the Ig heavy chain .mu. enhancer core. Sep., individual sites bind to the tetrameric complex with

affinities varying over a 100-fold range. However, when a low affinity site and a high affinity site are present on the same DNA mol., both are occupied at the same NF- $\mu$ .NR concn.; thus, there is a strong cooperative interaction between binding sites. The tetrameric structure provides a mechanism for binding cooperativity in which initial binding is mediated through a high affinity site on the DNA mol. followed by the engagement of the low affinity site juxtaposed to adjacent protein subunits. The presence of multiple binding sites flanking the  $\mu$ . enhancer core may reflect the influence of NF- $\mu$ .NR binding on enhancer three-dimensional structure, transcription factor binding, and/or nuclear matrix interactions for cell type-specific enhancer function.

L6 ANSWER 20 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1992:19542 CAPLUS

DN 116:19542

TI Anti-IgM antibodies down modulate  $\mu$ -enhancer activity of OTF2 levels in LPS-stimulated mouse splenic B-cells

AU Chen, Una; \*\*\*Scheuermann, Richard H.\*\*\* ; Wirth, Thomas; Gerster, Thomas; Roeder, Robert G.; Harshman, Keith; Berger, Christoph

CS Basel Inst. Immunol., Basel, CH-4005, Switz.

SO Nucleic Acids Res. (1991), 19(21), 5981-9

CODEN: NARHAD; ISSN: 0305-1048

DT Journal

LA English

AB Stimulation of small, resting, splenic B cells with bacterial lipopolysaccharide (LPS) induces proliferation, differentiation to plasma cell formation, and the expression of Ig heavy chain (IgH). When this is combined with agents which crosslink surface Ig, differentiation and the induction of surface immunoglobulin are suppressed even though proliferation proceeds. Anti- $\mu$  antibodies suppress Ig gene expression of transfected  $\mu$  constructs, even if either the membrane or secretory segments have been deleted. The effects of anti- $\mu$  treatment were examd. on the IgH enhancer (IgHE) attached to a heterologous test gene (CAT). The IgH enhancer alone was subject to anti- $\mu$  suppression, while the SV40 enhancer was insensitive. To det. what was responsible for suppression of enhancer function by anti- $\mu$ , nuclear exts. from stimulated splenic B cells were examd. for the presence of sequence-specific DNA binding activities to various sites within the enhancer. Two specific differences were found: an induction in  $\mu$ .E5 binding activity, and a redn. in octamer transcription factor 2 (OTF2) binding activity, after anti- $\mu$  treatment. Anal. of these cells by in situ immunofluorescence with anti-OTF2 antibodies suggests that the nuclear localization of OTF2 in anti- $\mu$  treated cells may change, as well as its abs. level.

L6 ANSWER 21 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1989:568485 CAPLUS

DN 111:168485

TI A developmental-specific factor binds to suppressor sites flanking the immunoglobulin heavy-chain enhancer

AU \*\*\*Scheuermann, Richard H.\*\*\* ; Chen, Una

CS Basel Inst. Immunol., Basel, 4005, Switz.

SO Genes Dev. (1989), 3(8), 1255-66  
CODEN: GEDEEP; ISSN: 0890-9369

DT Journal

LA English

AB A novel nuclear protein, NF-.mu.NR, that binds to multiple sites flanking the Ig heavy-chain enhancer was identified. The expression of NF-.mu.NR shows a unique developmental pattern; the activity is present in all cells representing early stages of B-cell development, but is absent from more mature cells that express a high level of Ig heavy chains. NF-.mu.NR also is present in most cell lines outside of the B-cell lineage (e.g., T cells, macrophages, and fibroblasts). The binding sites for NF-.mu.NR correlate very well with cis-acting neg. regulatory elements of the heavy chain enhancer defined previously. Indeed, when the segments bound by NF-.mu.NR are deleted from the enhancer, it functions as a pos. transcription element in T cells and macrophages. Taken together, these results suggest that NF-.mu.NR may function as a neg. regulator of enhancer function. The observation that the segments bound by NF-.mu.NR correspond to the segments bound to the nuclear matrix suggests an intriguing model not only of how enhancers might function but also of how neg. regulation might occur.

L6 ANSWER 22 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1988:432912 CAPLUS

DN 109:32912

TI UmuD mutagenesis protein of Escherichia coli: overproduction, purification, and cleavage by RecA

AU Burckhardt, Sabine E.; Woodgate, Roger; \*\*\*Scheuermann, Richard\*\*\*  
\*\*\* H \*\*\* ; Echols, Harrison

CS Dep. Mol. Biol., Univ. California, Berkeley, CA, 94720, USA

SO Proc. Natl. Acad. Sci. U. S. A. (1988), 85(6), 1811-15

CODEN: PNASA6; ISSN: 0027-8424

DT Journal

LA English

AB The mutation rate of E. coli increases .apprxeq.100-fold after treatment with replication-inhibiting agents such as UV light. This enhanced mutation rate requires the action of the UmuD and UmuC proteins, which are induced as part of the SOS response to DNA damage. To initiate a biochem. characterization of the role of these proteins, a plasmid system was developed that gives efficient expression of the umuD and umuC genes. The umuD and umuC genes were placed under the control of a regulated phage .lambda. PL promoter and a synthetic ribosome-binding site, and the distance to the UmuD start was adjusted to maximize gene expression. Starting from this overprodn. system, the authors purified the UmuD protein and studied its interaction with RecA. The SOS response is turned on by the capacity of RecA protein to mediate cleavage of the LexA repressor for SOS-controlled operons. Others have shown that UmuD exhibits sequence homol. to LexA around the cleavage site, suggesting a possible cleavage reaction for UmuD. Here it is shown that RecA mediates cleavage of UmuD, probably at this site. As with LexA, UmuD also undergoes a self-cleavage reaction. Apparently, RecA-mediated cleavage of UmuD is another role for RecA in SOS mutagenesis, probably activating UmuD for its mutagenic function.

L6 ANSWER 23 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1987:132593 CAPLUS

DN 106:132593

TI Replication fidelity in *Escherichia coli* by DNA polymerase III: the role of exonucleolytic editing in spontaneous and induced mutagenesis

AU \*\*\*Scheuermann, Richard Harvey\*\*\*

CS Univ. California, Berkeley, CA, USA

SO (1986) 147 pp. Avail.: Univ. Microfilms Int., Order No. DA8624926

From: Diss. Abstr. Int. B 1987, 47(7), 2773

DT Dissertation

LA English

AB Unavailable

L6 ANSWER 24 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1986:124012 CAPLUS

DN 104:124012

TI Capacity of RecA protein to bind preferentially to UV lesions and inhibit the editing subunit (.epsilon.) of DNA polymerase III: a possible mechanism for SOS-induced targeted mutagenesis

AU Lu, Chi; \*\*\*Scheuermann, Richard H.\*\*\* ; Echols, Harrison

CS Dep. Mol. Biol., Univ. California, Berkeley, CA, 94720, USA

SO Proc. Natl. Acad. Sci. U. S. A. (1986), 83(3), 619-23

CODEN: PNASA6; ISSN: 0027-8424

DT Journal

LA English

AB The RecA protein of *Escherichia coli* might participate in targeted mutagenesis by binding preferentially to the site of the DNA damage (e.g., pyrimidine dimer) because of its partially unwound character; DNA polymerase III (polIII) [37217-33-7] will then encounter RecA-coated DNA at the lesion and might replicate across the damaged site with reduced fidelity. Two major predictions of this model were analyzed at a biochem. level. With respect to lesion recognition, purified RecA protein bound more efficiently to UV-irradiated, double-stranded DNA than to nonirradiated DNA, as judged by filter-binding and gel electrophoresis assays. With respect to replication fidelity, RecA inhibited the exonuclease of the purified editing subunit of polIII, the .epsilon. protein. Apparently, the activities of RecA required for targeted mutagenesis are lesion recognition, followed by localized inhibition of the editing capacity of the .epsilon. subunit of polIII holoenzyme. In this proposed mechanism, 1 activation signal for RecA for mutagenesis is the lesion itself. Because UV-irradiated, double-stranded DNA efficiently activates RecA for cleavage of the LexA repressor, the lesion itself may also often serve as an activation signal for the induction of SOS-controlled genes.

L6 ANSWER 25 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1985:92085 CAPLUS

DN 102:92085

TI A separate editing exonuclease for DNA replication: the .epsilon. subunit of *Escherichia coli* DNA polymerase III holoenzyme

AU \*\*\*Scheuermann, Richard H.\*\*\* ; Echols, Harrison

CS Dep. Mol. Biol., Univ. California, Berkeley, CA, 94720, USA

SO Proc. Natl. Acad. Sci. U. S. A. (1984), 81(24), 7747-51  
CODEN: PNASA6; ISSN: 0027-8424

DT Journal

LA English

AB DNA polymerase III (I) holoenzyme of *E. coli* has 3'.fwdarw.5' exonuclease (editing) activity in addn. to its polymerase activity. The polymn. activity is known to be carried by the large .alpha. subunit, the product of the *dnaE* gene. Mutations affecting the fidelity of DNA replication in vivo and the activity of 3'.fwdarw.5' exonuclease assayed in vitro are found in the *dnaQ* gene, which specifies the .epsilon. subunit. To det. whether .epsilon. carries the 3'.fwdarw.5' exonuclease activity, an overprodn. protocol was used to purify .epsilon. sep. from the other subunits of I holoenzyme. The .epsilon. subunit has 3'.fwdarw.5' exonuclease activity indistinguishable from that of I core, the subassembly of I holoenzyme consisting of the .alpha., .epsilon., and .theta. subunits. Thus, the editing and polymn. activities of I holoenzyme reside on distinct subunits, in contrast to DNA polymerase I of *E. coli* and DNA polymerase of phage T4.

L6 ANSWER 26 OF 26 CAPLUS COPYRIGHT 1998 ACS

AN 1984:62621 CAPLUS

DN 100:62621

TI Identification of the .epsilon.-subunit of *Escherichia coli* DNA polymerase III holoenzyme as the *dnaQ* gene product: A fidelity subunit for DNA replication

AU \*\*\*Scheuermann, Richard\*\*\* ; Tam, Schuman; Burgers, Peter M. J.; Lu, Chi; Echols, Harrison

CS Dep. Mol. Biol., Univ. California, Berkeley, CA, 94720, USA

SO Proc. Natl. Acad. Sci. U. S. A. (1983), 80(23), 7085-9

CODEN: PNASA6; ISSN: 0027-8424

DT Journal

LA English

AB Based on extensive genetic and biochem. studies, the multisubunit DNA polymerase III [37217-33-7] holoenzyme is considered responsible for the chain-elongation stage in replication of the genome of *E. coli* and is thus expected to be the major determinant of fidelity as well. Previous expts. have shown that 2 mutations conferring a very high mutation rate on *E. coli*, *mutD5* and *dnaQ49*, decrease severely the 3'.fwdarw.5' exonucleolytic editing activity of the polymerase III holoenzyme. To identify more precisely the nature of these mutations, genetic mapping and complementation expts. were conducted. From these studies and expts. by others, it appears that the most potent general mutator mutations in *E. coli* occur in a single gene, *dnaQ*. To define further the role of the *dnaQ* gene, 2-dimensional gel electrophoresis was used to compare the labeled *dnaQ* gene product with purified polymerase III holoenzyme. The *dnaQ* product comigrates with the .epsilon.-subunit, a 25-kilodalton protein of the polymerase III core enzyme. Thus, the .epsilon.-subunit of polymerase III holoenzyme has a special role in defining the accuracy of DNA replication, probably through control of the 3'.fwdarw.5' exonuclease activity.

=> e uhr jonathan w/au

E1 1 UHR JOHN J/AU  
E2 4 UHR JONATHAN/AU  
E3 178 --> UHR JONATHAN W/AU  
E4 1 UHR JONATHAN WILLIAM/AU  
E5 1 UHR JONATHON W/AU  
E6 17 UHR L/AU  
E7 1 UHR L E/AU  
E8 1 UHR LARS ERIC/AU  
E9 54 UHR M/AU  
E10 24 UHR M L/AU  
E11 43 UHR M R/AU  
E12 3 UHR MANFRED/AU

=> s e2-e5

7 184 ("UHR JONATHAN"/AU OR "UHR JONATHAN W"/AU OR "UHR JONATHAN  
WILLIAM"/AU OR "UHR JONATHON W"/AU)

=> dup rem l7

PROCESSING COMPLETED FOR L7

L8 184 DUP REM L7 (0 DUPLICATES REMOVED)

=> s l8 and erbb2

L9 1 L8 AND ERBB2

=> s l8 and (erbb2 or her2)

L10 1 L8 AND (ERBB2 OR HER2)

=> d bib ab

L10 ANSWER 1 OF 1 CAPLUS COPYRIGHT 1998 ACS

AN 1998:268615 CAPLUS

DN 128:307524

TI Antibodies to the neu receptor capable of inducing apoptosis and  
their therapeutic uses

IN Fendly, Brian M.; Phillips, Gail Dianne; Scheuermann, Richard H.;  
\*\*\*Uhr, Jonathan W.\*\*\*

PA Genentech, Inc., USA; Board of Regents, the University of Texas  
System

SO PCT Int. Appl., 77 pp.

CODEN: PIXXD2

PI WO 9817797 A1 19980430

DS W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,  
DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR,  
KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,  
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG,  
UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB,  
GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG

AI WO 97-US18385 19971009

PRAI US 96-731794 19961018

DT Patent

LA English

AB Anti- \*\*\*ErbB2\*\*\* antibodies that bind to an epitope in Domain 1  
of the receptor (the neu receptor) and induce cell death via  
apoptosis are described. These antibodies have a no. of uses, e.g.  
in the treatment of ovarian cancer and in detection of  
overexpression of the \*\*\*erbB2\*\*\* gene.

=> s erbb2 or her2

L12 5699 ERBB2 OR HER2

=> s erbb2

L13 4246 ERBB2  
=> s l13 and antibod?  
5 FILES SEARCHED...  
L14 957 L13 AND ANTIBOD?  
=> s l14 and apopto?  
L15 32 L14 AND APOPTO?  
=> dup rem l15  
PROCESSING COMPLETED FOR L15  
L16 16 DUP REM L15 (16 DUPLICATES REMOVED)  
=> d bib ab 1-  
YOU HAVE REQUESTED DATA FROM 16 ANSWERS - CONTINUE? Y/(N):y

L16 ANSWER 1 OF 16 CAPLUS COPYRIGHT 1998 ACS  
AN 1998:293396 CAPLUS  
DN 129:3862  
TI Enhancement of tumor cell chemosensitivity and radiosensitivity  
using single chain intracellular \*\*\*antibodies\*\*\*  
IN Buchsbaum, Donald J.; Curiel, David T.; Stackhouse, Murray  
PA UAB Research Foundation, USA  
SO PCT Int. Appl., 95 pp.  
CODEN: PIXXD2  
PI WO 9818489 A1 19980507  
DS W: AU, CA, JP  
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,  
SE  
AI WO 97-US19911 19971030  
PRAI US 96-29673 19961030  
DT Patent  
LA English  
AB The present invention provides a method of enhancing the  
chemosensitivity and radiosensitivity of a neoplastic cell  
expressing an oncoprotein that stimulates proliferation of the cell.  
Abrogation of tumor cell resistance is achieved by transfection with  
a nucleic acid mol. encoding an scFv \*\*\*antibody\*\*\* homolog,  
wherein the homolog is expressed intracellularly and binds to the  
oncoprotein in the endoplasmic reticulum. An intracellular  
single-chain \*\*\*antibody\*\*\*, directed to the erbB-2 oncoprotein,  
is shown to down-regulate its surface expression in breast and  
ovarian carcinoma cells lines and increase the sensitivity to  
cisplatin and x-irradn.

L16 ANSWER 2 OF 16 CAPLUS COPYRIGHT 1998 ACS  
AN 1998:268615 CAPLUS  
DN 128:307524  
TI \*\*\*Antibodies\*\*\* to the neu receptor capable of inducing  
\*\*\*apoptosis\*\*\* and their therapeutic uses  
IN Fendly, Brian M.; Phillips, Gail Dianne; Scheuermann, Richard H.;  
Uhr, Jonathan W.  
PA Genentech, Inc., USA; Board of Regents, the University of Texas  
System  
SO PCT Int. Appl., 77 pp.  
CODEN: PIXXD2  
PI WO 9817797 A1 19980430  
DS W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,  
DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR,

KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,  
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG,  
UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB,  
GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG

AI WO 97-US18385 19971009

PRAI US 96-731794 19961018

DT Patent

LA English

AB Anti- \*\*\*ErbB2\*\*\* \*\*\*antibodies\*\*\* that bind to an epitope in  
Domain 1 of the receptor (the neu receptor) and induce cell death  
via \*\*\*apoptosis\*\*\* are described. These \*\*\*antibodies\*\*\*  
have a no. of uses, e.g. in the treatment of ovarian cancer and in  
detection of overexpression of the \*\*\*erbB2\*\*\* gene.

L16 ANSWER 3 OF 16 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 1

AN 98:364727 BIOSIS

DN 01364727

TI Bcl2 and p53 protein expression in metastatic carcinoma of unknown  
primary origin: Biological and clinical implications. A Hellenic  
Co-operative Oncology Group Study.

AU Briasoulis E; Tsokos M; Fountzilas G; Bafaloukos D; Kosmidis P;  
Samantas E; Skarlos D; Nicolaides C; Pavlidis N

CS Oncol. Sect., Dep. Med., Medical Sch., Ioannina Univ., Ioannina  
45110, Greece

SO Anticancer Research 18 (3B). 1998. 1907-1914. ISSN: 0250-7005

LA English

AB We have previously shown that metastatic carcinomas of unknown  
primary site overexpress several tumour markers as well as the  
products of the oncogenes c-myc, ras and c- \*\*\*erbB2\*\*\*. We  
analysed the tissue expression of the protein products of the  
\*\*\*apoptosis\*\*\* modulation genes p53 and bcl-2 in 47 CUP cases.  
Formalin-fixed, paraffin embedded tumour specimens were stained with  
commercially available \*\*\*antibodies\*\*\* to p53 (DO7) and bcl-2  
after antigen retrieval by the microwave method. Staining was  
evaluated by intensity (1+ to 3+), percentage of positive cells  
(1-100%), and the 'intensity times percentage' product defined as the  
immunoreactivity index with values ranging from 0 to 300.  
Immunoreactivity index values higher than 150 were considered to  
characterize protein overexpression. Expression of p53 was identified  
in 70.2% of tumours while 53% of them showed a high immunoreactivity  
index. Bcl-2 expression was detected in 65% of tumours and  
overexpressed in 40%. Overexpression of both proteins was detected in  
20% of tumours. The detection of either protein was not associated  
with any of the major clinicopathological variables studied.  
Nevertheless, a trend towards a more favourable response to platin  
based chemotherapy was seen in the cases that showed a strong  
expression of both proteins, when analysed by immunoreactivity index  
and percentage of Positive cells. We conclude that CUP overexpress at  
a high percentage the p53 and the bcl-2 proteins. The observed weak  
association of strong expression of these proteins with response to  
platin-based chemotherapy deserves further evaluation in the CUP  
setting.

L16 ANSWER 4 OF 16 CAPLUS COPYRIGHT 1998 ACS



AN 1998:367345 CAPLUS

DN 129:121403

TI Human tumor growth suppression by \*\*\*apoptosis\*\*\* induced with anti-ErbB-2 chimeric monoclonal \*\*\*antibody\*\*\*

AU Sasaki, Shigeru; Tsujisaki, Masayuki; Jinnohara, Tsuneharu; Ishida, Tadao; Sekiya, Masuo; Adachi, Masaaki; Takahashi, Shuji; Hinoda, Yuji; Imai, Kohzoh

CS First Department of Internal Medicine, Sapporo Medical University, Sapporo, 060, Japan

SO Jpn. J. Cancer Res. (1998), 89(5), 562-570

CODEN: JJCREP; ISSN: 0910-5050

PB Japanese Cancer Association

DT Journal

LA English

AB The authors established an anti-ErbB-2 mouse-human chimeric monoclonal \*\*\*antibody\*\*\* (MoAb), CH401, which was able to kill cancer cells overexpressing the ErbB-2 protein in vitro. The anal. of the killing mechanism indicated that MoAb CH401 might be the first anti-ErbB-2 mouse-human chimeric MoAb which can induce the \*\*\*apoptosis\*\*\* of cancer cells, since morphol. changes and DNA fragmentation were recognized in MoAb CH401-treated cells. The ErbB-2 receptor appears to have two opposing functions: acting as a receptor both for a growth factor and for an \*\*\*apoptotic\*\*\* factor. The results indicate that MoAb CH401 treatment may prove to be very useful for cancer therapy.

L16 ANSWER 5 OF 16 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 2

AN 98:306103 BIOSIS

DN 01306103

TI The level of \*\*\*erbB2\*\*\* expression predicts sensitivity to the cytotoxic effects of an intracellular anti- \*\*\*erbB2\*\*\* sFv.

AU Grim J; Deshane J; Siegal G P; Alvarez R D; Difiore P; Curiel D T

CS Dep. Pathol., Univ. Ala., Birmingham, AL 35294, USA

SO Journal of Molecular Medicine (Berlin) 76 (6). 1998. 451-458. ISSN: 0946-2716

LA English

AB We have previously demonstrated that an intracellular \*\*\*antibody\*\*\* (sFv) directed against \*\*\*erbB2\*\*\* can achieve a specific cytotoxicity in \*\*\*erbB2\*\*\* overexpressing cancer cells of varying histogenesis. In order to further delineate the mechanistic basis of the induced \*\*\*apoptosis\*\*\*, transient and stable cotransfections were performed. Transient cotransfection of \*\*\*erbB2\*\*\* mutant and chimeric molecules demonstrated that the cytoplasmic domain of \*\*\*erbB2\*\*\*, or the homologous cytoplasmic domain of the epidermal growth factor receptor, is required for \*\*\*apoptosis\*\*\* induction. These results were confirmed in assays utilizing differential derivation of stable clones. To examine the effects of varying ratios of the anti- \*\*\*erbB2\*\*\* sFv and its target \*\*\*erbB2\*\*\* we performed additional cotransfection experiments in \*\*\*erbB2\*\*\* negative target cells. When \*\*\*erbB2\*\*\* levels are held constant, observed cytotoxicity is proportional to the amount of sFv added. In addition, when sFv levels are held constant, increasing levels of cotransfected \*\*\*erbB2\*\*\* can overcome the \*\*\*apoptotic\*\*\* response. These results indicate that a minimal threshold level of the sFv and its target are required

to induce cytotoxicity. To examine this phenomenon in an \*\*\*erbB2\*\*\* positive cell line, SKOV3 ovarian carcinoma cells were utilized to derive a stable clone expressing low levels of sFv. When this cell line was compared to the parental SKOV3 cell line, it was shown that less exogenous sFv was needed to induce cytotoxicity in the clone already expressing low levels of sFv, indicating that endogenous and exogenous levels of sFv are additive. In summary, the results presented here indicate that the carboxy-terminus of the intracellular domain of the \*\*\*erbB2\*\*\* molecule is involved in the induction of \*\*\*apoptosis\*\*\*. Furthermore, the expression levels of the sFv and its target protein need to overcome a threshold level in order to achieve a cytotoxic response.

L16 ANSWER 6 OF 16 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 3

AN 98:123384 BIOSIS

DN 01123384

TI Bcl-2 immunohistochemistry in a surgical series of non-small cell lung cancer patients.

AU Fleming M V; Guinee D G Jr; Chu W S; Freedman A N; Caporaso N E; Bennett W P; Colby T V; Tazelaar H; Abbondanzo S L; Jett J; Pairorero P; Trastek V; Liotta L A; Harris C C; Travis W D

CS Dep. Pulmonary Mediastinal Pathol., Armed Forces Inst. Pathol., 6825 16th St, NW, Bldg. 54, Room M003B, Washington, DC 20306-6000, USA

SO Human Pathology 29 (1). 1998. 60-64. ISSN: 0046-8177

LA English

AB The bcl-2 gene is implicated in oncogenesis by its ability to prolong cell survival through the inhibition of \*\*\*apoptosis\*\*\*, without increasing cell proliferation. An association between immunohistochemical staining for bcl-2 protein and the histological type and Prognosis Of non-small cell Carcinoma was hypothesized by Pezzella et al. (N Engl J Med 329:690-694, 1993). In a case series, we stained formalin-fixed, paraffin-embedded tumor tissue from 106 surgical non-small cell lung cancer patients with an \*\*\*antibody\*\*\* to bcl-2 protein (DAKO clone 124, Carpinteria, CA). The resulting bcl-2 staining data were evaluated for associations with demographic, histological, immunohistochemical, and genetic features, including p53 mutations. Bcl-2 staining was observed in tumors from 29 of 106 (27%) of subjects, but was significantly less frequent in subjects' adenocarcinoma histology (8 of 55, 14.6%) (P = .007). This finding persisted after adjustment for age, gender, stage, grade, smoking history, and disease-free survival. In univariate analyses, no association was seen with age, weight, body mass index, gender, or pack-years smoking; tumor grade, stage, or patient performance status; p53 or c- \*\*\*erbB2\*\*\* immunohistochemical staining, or p53 mutations. These data agree with earlier reports that bcl-2 staining is less common in adenocarcinomas; however, our data do not support the hypothesis that bcl-2 staining confers a better prognosis overall, in squamous cell carcinoma, or in an older patient population.

L16 ANSWER 7 OF 16 SCISEARCH COPYRIGHT 1998 ISI (R)

AN 97:669317 SCISEARCH

GA The Genuine Article (R) Number: XU396

TI Neu differentiation factor induces \*\*\*ErbB2\*\*\* down-regulation and \*\*\*apoptosis\*\*\* of \*\*\*ErbB2\*\*\* -overexpressing breast

tumor cells

AU Daly J M; Jannot C B; Beerli R R; GrausPorta D; Maurer F G; Hynes N  
E (Reprint)

CS FRIEDRICH MIESCHER INST, POB 2543, CH-4002 BASEL, SWITZERLAND  
(Reprint); FRIEDRICH MIESCHER INST, CH-4002 BASEL, SWITZERLAND  
CYA SWITZERLAND

SO CANCER RESEARCH, (1 SEP 1997) Vol. 57, No. 17, pp. 3804-3811.

Publisher: AMER ASSOC CANCER RESEARCH, PUBLIC LEDGER BLDG, SUITE  
816, 150 S. INDEPENDENCE MALL W., PHILADELPHIA, PA 19106.

ISSN: 0008-5472.

DT Article; Journal

FS LIFE; CLIN

LA English

REC Reference Count: 56

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB New differentiation factor (NDF), a member of the epidermal  
growth factor (EGF)-related peptide family, activates \*\*\*ErbB2\*\*\*  
via heterodimerization with the NDF receptors ErbB3 and ErbB4. In a  
similar fashion, EGF receptor (EGFR) agonists induce heterodimers of  
EGFR and \*\*\*ErbB2\*\*\*. In this paper, we show that the  
\*\*\*ErbB2\*\*\*-overexpressing breast tumor cells SKBR3, AU565, and  
MDA-MB453 are growth inhibited by NDF. Cells with elevated levels of  
\*\*\*ErbB2\*\*\* but little or no NDF receptors (SKOV3 and MDA-MB361)  
or cells with low levels of \*\*\*ErbB2\*\*\* (T47D and MCF7) are not  
growth inhibited. None of the EGFR agonists tested (EGF,  
beta-cellulin, or heparin-binding EGF) inhibited growth of  
\*\*\*ErbB2\*\*\*-overexpressing cells. These results suggest that  
formation of an \*\*\*ErbB2\*\*\* /NDF receptor heterodimer, but not of  
an \*\*\*ErbB2\*\*\* /EGFR heterodimer, promotes growth inhibition. In  
addition, NDF caused a down-regulation of \*\*\*ErbB2\*\*\* but not of  
ErbB3. The mechanism underlying the inhibitory effect was examined  
further in SKBR3 cells, which are 95% growth inhibited by NDF. A  
G(2)-M arrest is seen 24 h after NDF treatment, and increased  
\*\*\*apoptosis\*\*\* is detectable from day 2 onward. The results  
demonstrate for the first time that NDF induces \*\*\*apoptosis\*\*\*  
of tumor cells overexpressing \*\*\*ErbB2\*\*\*.

L16 ANSWER 8 OF 16 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 4

AN 97:214509 BIOSIS

DN 99521013

TI An intracellular anti-erbB-2 single-chain \*\*\*antibody\*\*\* is  
specifically cytotoxic to human breast carcinoma cells overexpressing  
erbB-2.

AU Wright M; Grim J; Deshane J; Kim M; Strong T V; Siegal G P; Curiel D  
T

CS Univ. Ala., Gene Ther. Program, 1824 6th Ave. South, Room WTI 620,  
Birmingham, AL 35294, USA

SO Gene Therapy 4 (4). 1997. 317-322. ISSN: 0969-7128

LA English

AB We previously demonstrated that delivery of a gene encoding an  
anti-erbB-2 intracellular single-chain \*\*\*antibody\*\*\* (sFv)  
resulted in down-regulation of cell surface erbB-2 levels and  
induction of \*\*\*apoptosis\*\*\* in erbB-2 overexpressing ovarian  
cancer cells. Based upon these findings, we hypothesized that human  
breast carcinomas overexpressing erbB-2 would be similarly affected

by this genetic intervention. We evaluated the phenotypic effects resulting from intracellular expression of the anti-erbB-2 sFv on the human breast cancer cell lines MDA-MB-361, SK-BR-3, BT-474, MCF-7 and MDA-MB-231. Recombinant adenoviruses encoding either a reporter gene (AdCMVLacZ) or the endoplasmic reticulum (ER) directed anti-erbB-2 sFv (Ad21) were delivered to various breast cancer cell lines. Cell viability was determined by a proliferation assay and fluorescent microscopy allowed visualization of \*\*\*apoptotic\*\*\* cells. An erbB-2 ELISA quantified the endogenous \*\*\*erbB2\*\*\* levels of each cell line. The anti-erbB-2 sFv-encoding-adenovirus, Ad21, but not the beta-galactosidase encoding adenovirus, AdCMVLacZ, was cytotoxic to gt 95% of the tumor cells in the MDA-MB-361 and SK-BR-3 lines, and gt 60% of the tumor cells in the BT-474 line. In marked contrast, the MCF-7 and MDA-MB-231 cell lines showed no change in the rate of cell proliferation following this treatment. The cytotoxic effects generated in the first three lines were a consequence of the induction of \*\*\*apoptosis\*\*\* by the anti-erbB-2 sFv. An ELISA specific for erbB-2 showed that the breast cancer cell lines most susceptible to the anti-erbB-2 sFv, MDA-MB-361, SK-BR-3 and BT-474, overexpressed the erbB-2 protein while the cell lines demonstrating no response to the anti-erbB-2 sFv, MCF-7 and MDA-MB-231, expressed the lowest levels of erbB-2. These results demonstrate that targeted killing of erbB-2 overexpressing cells via intracellular knockout can be accomplished in the context of breast carcinoma. Furthermore, erbB-2 levels in breast tumor cells may be predictive of their sensitivity to sFv-mediated killing. The ability to accomplish selective cytotoxicity of breast cancer cell lines overexpressing the erbB-2 tumor marker should allow for derivation of clinical gene therapy strategies for breast cancer utilizing this approach.

L16 ANSWER 9 OF 16 MEDLINE

AN 97148578 MEDLINE

DN 97148578

TI Fas-signaling and effects on receptor tyrosine kinase signal transduction in human breast epithelial cells.

AU Shen K; Novak R F

CS Institute of Chemical Toxicology and Karmanos Cancer Institute, Wayne State University, Detroit, Michigan 48201, USA.

NC ES02521 (NIEHS)

ES06639 (NIEHS)

SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1997 Jan 3) 230 (1) 89-93.

Journal code: 9Y8. ISSN: 0006-291X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199704

AB Fas-mediated cell death was examined in MCF-10AT preneoplastic human breast epithelial cells. Treatment with anti-Fas for 48 h induced \*\*\*apoptosis\*\*\* with cells exhibiting typical \*\*\*apoptotic\*\*\* features including loss of cell contact, condensation of chromatin, and increased staining of the nuclear membrane. DNA fragmentation occurred in response to anti-Fas treatment. Anti-Fas treatment resulted in decreased p53 protein levels, while bcl-2 and bax

protein levels remained unaffected. Cells treated with anti-Fas also exhibited increased tyrosine phosphorylation of the c-met growth factor receptor tyrosine kinase. Immunoprecipitation experiments demonstrated that Fas associated with c- \*\*\*erbB2\*\*\* and c-met in untreated cells. Treatment with anti-Fas, however, significantly decreased Fas-c- \*\*\*erbB2\*\*\* and Fas-c-met association. Anti-Fas treatment of these cells caused a significant decrease in p120-GAP levels, ERK-1 levels, and phosphorylation, as well as Grb2-Sos1 and MEK-1-ERK-1 association. These results show that Fas-signaling exerted a suppressive effect on p53 levels and on downstream effectors of receptor tyrosine kinase signal transduction, thereby ensuring cell death.

L16 ANSWER 10 OF 16 CAPLUS COPYRIGHT 1998 ACS

AN 1996:575230 CAPLUS

DN 125:245181

TI erbB-2 knockout employing an intracellular single-chain \*\*\*antibody\*\*\* (sFv) accomplishes specific toxicity in erbB-2-expressing lung cancer cells

AU Grim, Jon; Deshane, Jessy; Feng, Meizhen; Lieber, Andre; Kay, Mark; Curiel, David T.

CS Gene Therapy program, Univ. Alabama, Birmingham, AL, USA

SO Am. J. Respir. Cell Mol. Biol. (1996), 15(3), 348-354

CODEN: AJRBEL; ISSN: 1044-1549

DT Journal

LA English

AB ErbB-2 is known to be overexpressed in several human malignancies including lung cancer. Because of its role in neoplastic transformation as well as its assocn. with poor prognosis, this oncogene has been targeted through various anti-cancer methodologies. In this regard, we have recently demonstrated that erbB-2-overexpressing ovarian tumor cell lines transfected with an endoplasmic reticulum form of an anti-erbB-2 single-chain \*\*\*antibody\*\*\* undergo a specific cytotoxicity through the induction of \*\*\*apoptosis\*\*\*. Since certain forms of lung cancer are also assocd. with overexpression of erbB-2, we evaluated the use of this novel therapeutic in this context. For these studies, several human lung adenocarcinoma cell lines were stably and transiently transfected with the anti-erbB-2 sFv gene. We demonstrate here that the anti-erbB-2 sFv can cause specific cytotoxicity in lung cancer cells. As a first step toward clin. translation of this strategy, we constructed a replication-deficient recombinant adenoviral vector expressing the anti-erbB-2 sFv construct. We further demonstrate that our anti-erbB-2 sFv-encoding adenoviral vector can accomplish high levels of cytotoxicity in lung cancer cells. Based on these results, it is proposed that this strategy of oncoprotein ablation may have use in the treatment of some forms of human lung cancer.

L16 ANSWER 11 OF 16 CAPLUS COPYRIGHT 1998 ACS

AN 1996:285777 CAPLUS

DN 124:340442

TI Intracellular \*\*\*antibody\*\*\* against erbB-2 mediates targeted tumor cell eradication by \*\*\*apoptosis\*\*\*

AU Deshane, Jessy; Grim, Jon; Loechel, Steve; Siegal, Gene P.; Alvarez,

Ronald D.; Curiel, David T.  
CS Department Obstetrics and Gynecology, University Alabama,  
Birmingham, AL, USA

SO Cancer Gene Ther. (1996), 3(2), 89-98

CODEN: CGTHEG; ISSN: 0929-1903

DT Journal

LA English

AB Methods were developed to achieve targeted eradication of the erbB-2 oncoprotein using gene constructs encoding anti-erbB-2 intracellular single-chain \*\*\*antibodies\*\*\*. This method of genetic intervention caused a marked cytotoxic effect in erbB-2-overexpressing human ovarian tumor cells. Evaluation of the mechanistic basis of this phenomenon demonstrated that programmed cell death had been induced. Significantly, no cytotoxic effect was obsd. in non-erbB-2-overexpressing tumors. The induction of \*\*\*apoptosis\*\*\* could be shown to be secondary to the intracellular \*\*\*antibody\*\*\*-mediated ectopic localization of the erbB-2 oncoprotein. Thus, the strategy of selective oncogene "knock-out" using intracellular \*\*\*antibodies\*\*\* represents a novel anticancer gene therapy strategy that offers the potential to achieve highly specific, targeted eradication of human tumor cells.

L16 ANSWER 12 OF 16 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 5

AN 96:481666 BIOSIS

DN 99196922

TI ErbB receptor activation, cell morphology changes, and

\*\*\*apoptosis\*\*\* induced by anti-Her2 monoclonal \*\*\*antibodies\*\*\*

AU Kita Y; Tseng J; Horan T; Wen J; Philo J; Chang D; Ratzkin B;

Pacifici R; Brankow D; Hu S; Luo Yi; Wen D; Arakawa T; Nicolson M

CS Dep. Immunol., Amgen Inc., Amgen Cent., Thousand Oaks, CA 91320, USA

SO Biochemical and Biophysical Research Communications 226 (1). 1996.

59-69. ISSN: 0006-291X

LA English

AB A panel of mAbs were generated against the purified soluble form of \*\*\*erbB2\*\*\* /Her2 receptor, corresponding to the extracellular region of the receptor, and examined for their ability to mimic the receptor ligand. Some of the mAbs strongly induced tyrosine phosphorylation of 180-185 kDa proteins, including not only Her2 but also Her3 and Her4 receptors, when they were expressed on the surface of breast cancer cells. These mAbs do not cross-react with Her3 or Her4 as demonstrated by competition study. Receptor phosphorylation was also observed with the cell lines transfected with Her2 or a chimeric receptor consisting of the extracellular domain of Her2 and the transmembrane and cytoplasmic domains of epidermal growth factor receptor. Selected mAbs were tested for their ability to change cell morphology, and one specific mAb, mAb74, induced cell morphology changes and \*\*\*apoptosis\*\*\*.

L16 ANSWER 13 OF 16 BIOSIS COPYRIGHT 1998 BIOSIS

AN 96:254290 BIOSIS

DN 98810419

TI Fas induced cell-death in the MCF-10A series human breast epithelial cells.

AU Shen K; Novak R F

QP 501.6 B43  
Adams

CS Inst. Chem. Tox., Wayne State Univ., Detroit, MI 48201, USA  
SO 87th Annual Meeting of the American Association for Cancer Research,  
Washington, D.C., USA, April 20-24, 1996. Proceedings of the American  
Association for Cancer Research Annual Meeting 37 (0). 1996. 26.  
ISSN: 0197-016X

DT Conference  
LA English

L16 ANSWER 14 OF 16 BIOSIS COPYRIGHT 1998 BIOSIS  
AN 95:288132 BIOSIS  
DN 98302432

TI Intracellular \*\*\*antibody\*\*\* knockout of the \*\*\*erbB2\*\*\*  
oncoprotein achieves targeted eradication of tumor targets by  
induction of \*\*\*apoptosis\*\*\* .

AU Deshane J; Grim J; Feng M; Kay M; Siegal G; Alvarez R; Curiel D  
CS Gene Therapy Program, Comprehensive Cancer Cent., Dep. Pathol., Univ.  
Alabama at Birmingham, Birmingham, AL, USA  
SO Clinical Research Meeting, San Diego, California, USA, May 5-8, 1995.  
Journal of Investigative Medicine 43 (SUPPL. 2). 1995. 328A.

DT Conference  
LA English

L16 ANSWER 15 OF 16 SCISEARCH COPYRIGHT 1998 ISI (R)  
AN 95:575531 SCISEARCH

GA The Genuine Article (R) Number: RQ689

TI INTRACELLULAR \*\*\*ANTIBODY\*\*\* KNOCKOUT OF THE \*\*\*ERBB2\*\*\*  
ONCOPROTEIN ACHIEVES TARGETED CYTOTOXICITY OF TUMOR TARGETS BY  
INDUCTION OF \*\*\*APOPTOSIS\*\*\*

AU DESHANE J (Reprint); GRIM J; FENG M; KAY M; SIEGAL G; ALVAREZ R;  
CURIEL D

CS UNIV ALABAMA, CTR COMPREHENS CANC, GENE THERAPY PROGRAM, BIRMINGHAM,  
W MIDLANDS, ENGLAND; WASHINGTON UNIV, ST LOUIS, MO, 63130

CYA ENGLAND; USA

SO AIDS RESEARCH AND HUMAN RETROVIRUSES, (1995) Vol. 11, Supp. 1, pp.  
S172.

ISSN: 0889-2229.

DT Conference; Journal  
FS LIFE  
LA ENGLISH  
REC No References

L16 ANSWER 16 OF 16 BIOSIS COPYRIGHT 1998 BIOSIS  
AN 94:47217 BIOSIS  
DN 97060217

TI The role of the \*\*\*erbB2\*\*\* receptor and its ligands in human  
breast cancer.

AU Lipman M E; Lupu R

CS Lombardi Cancer Res. Cent., Georgetown Univ. Med. Cent., Washington,  
DC 20007, USA

SO Annual Meeting of the Society for Biological Therapy, Nashville,  
Tennessee, USA, November 10-14, 1993. Journal of Immunotherapy 14  
(4). 1993. 369. ISSN: 1053-8550

DT Conference  
LA English

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